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Identification and Structure−Activity Relationships of Chromene-Derived Selective Estrogen Receptor Modulators for Treatment of Postmenopausal Symptoms

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As part of a program aimed at the development of selective estrogen receptor modulators (SERMs), novel chromene scaffolds, benzopyranobenzoxapanes, were discovered. Many compounds showed binding affinity as low as 1.6−200 nM, displayed antagonist behaviors in the MCF-7 human breast adenocarcinoma cell line as well in Ishikawa cell line with IC_{50} values in the range 0.2−360 nM. On the basis of the side chain substitution, various compounds demonstrated strong inhibitory activity in anti-uterotropic assay. Compound **7**-(*R*) and its major metabolites **5**-(*R*) and **6**-(*R*) were evaluated in several in vivo models of estrogen action. Relative to a full estrogen agonist (ethynyl estradiol) and the SERM raloxifene, **7**-(*R*) was found to be a potent SERM that behaved as antagonist in the uterus and exhibited estrogen agonistic activity on bone, plasma lipids, hot flush, and vagina. The overall pharmacokinetic profile and stability were significantly improved compared to those of the phase 2 development compound **9**-(*R*).

Introduction

The endogenous steroid estrogen is a critical mediator of many physiological functions related to development, growth, and maintenance of a large number of tissues in both females and males. Selective estrogen receptor modulators (SERMs[a]) are compounds that act as estrogen agonists on selected targets while being estrogen antagonists on others.[1] Hot flush and vaginal dryness are the most common symptoms associated with menopause in women. Hot flush is characterized by the sudden onset of hot feeling, sweating, palpitation, and anxiety and affects approximately 75% of women as they enter menopause.[2] More than 50% of postmenopausal women experience lack of vaginal lubrication that leads to several genital complaints associated with a diminished frequency of all forms of sexual behavior.[3] Indeed, hormone therapy (HT) alleviates both of these symptoms in 80−90% of women and has been recognized as the most effective treatment for hot flush and vaginal dryness.[4] Despite the effectiveness of HT on these symptoms as well as the beneficial effects on bone and plasma cholesterol levels, its use has been limited because of side effects such as vaginal bleeding, breast tenderness, concerns about increased risks of breast cancer, and more recently, the concerns about cardiovascular safety in about 25% of patients. Given the clinical evidence that HT has an unfavorable benefit/risk ratio, there is an intense need for an alternative therapy for hot flush and vaginal dryness. Both tamoxifen (TAM) and raloxifene (RAL) have shown their high therapeutic potential for estrogen-related diseases. Thus, TAM, the first SERM approved for breast cancer, is effective for all stages of hormone-dependent breast cancer, whereas RAL is indicated for the prevention and treatment of osteoporosis in postmenopausal women.[5] These SERMs have beneficial effects on bone and lipid metabolism while antagonizing the effects of estrogens on the uterus and breasts. However, there are no SERMs that have been reported to have a clinical beneficial effect on hot flush and vaginal dryness.[4b,6]

Compound **9**-(*R*) is a SERM previously reported by our group that has an improved preclinical profile compared to SERMs that are currently marketed or are in late stage development.[7a] These improvements include the ability to protect against hot flushes and to improve vaginal fluidity in rodent models. These unique activities accompany the ability to protect against bone loss, lower plasma cholesterol levels, and block estrogen action in the breast and uterus, which are properties of the current SERMs. In spite of the unique pharmacological profile of compound **9**-(*R*), there are limitations to the molecule. First, it is a prodrug, i.e., pivalate groups on the A and D rings of the benzopyran backbone of the molecule are prone to hydrolysis by esterase.[7] Second, there are issues with the stability of the active metabolite and some of the intermediates in the synthesis of compound **9**-(*R*).[7b] In this article, we present structure−activity relationship of a novel chromene derived SERM and identification of a compound **7**-(*R*) as a backup NCE candidate for our clinical compound **9**-(*R*) with potential to move into clinical trials. The compound maintains the preclinical profile of our lead compound **9**-(*R*) and has improved stability, pharmacokinetic, and pharmacological properties (Figure 1).

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[a] Abbreviations: ER, estrogen receptor; HRT, hormone replacement therapy; SERM, selective estrogen receptor modulator; TAM, tamoxifen; RAL, raloxifene.

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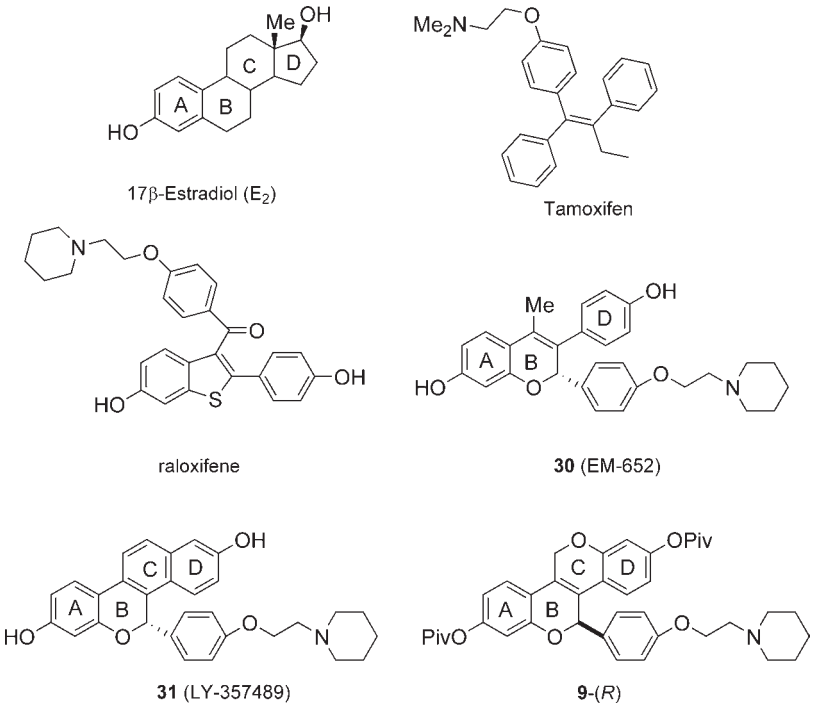


Figure 1. Structures of estradiol and representative SERMs.

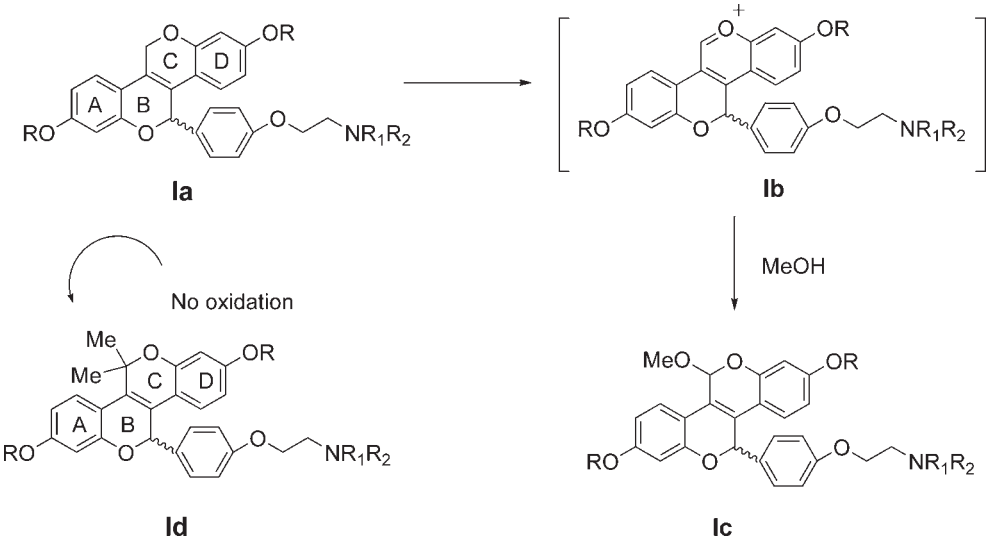


Figure 2. Degradation mechanisms of bisbenzopyran **I**.

Results and Discussion

Our working hypothesis is that SERMs with beneficial effects on hot flush and potentially vaginal dryness (i.e., agonists on these tissues) should have a conformation flexibility in the C/D region similar to that of the natural ligand 17β-estradiol. In **30** (EM-652) the D ring is connected to the B ring with a rotatable bond and hence can adopt various conformations.[5c] In contrast, **31** (LY-357489) is a planar structure in this region. We envisioned that structures possess flexibility in the C/D region between that of **30** and **31** might offer distinct pharmacological profiles.[5d] In other words, the former may be too flexible in the C/D region while the latter might too rigid. In our previous communication, we had reported that novel chromene-derived bisbenzopyrans where C=C bond in the C ring of **31** was replaced with a $-CH_2-O-$ linker resulted in a unique pharmacological profile, relieving hot flush as well as vaginal dryness while having beneficial effects on bone and lipids in preclinical animal models. However, some bisbenzopyran analogues with hydroxyl groups on both ends of the molecules such as **Ia** were found to be unstable in air, in light, and at elevated temperature.[7b] We discovered that after prolonged dissolution in methanol for an extended time, the methylene group in bisbenzopyran **Ia** was substituted with a methoxy group to yield **Ic**. We reasoned that the formation of the oxonium **Ib** is the major mechanism for the instability. In structure **Ib**, the aromatic character and the resonance contribution from the D ring stabilize the oxonium ion. We explored ways to block the oxidation process by introducing *gem*-dimethyls to the methylene group.[7b] Although the oxidation was prevented, **Id** did

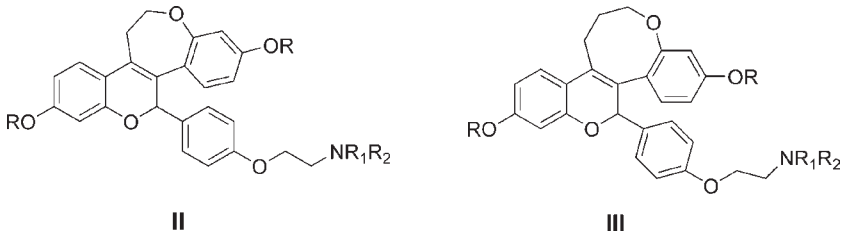
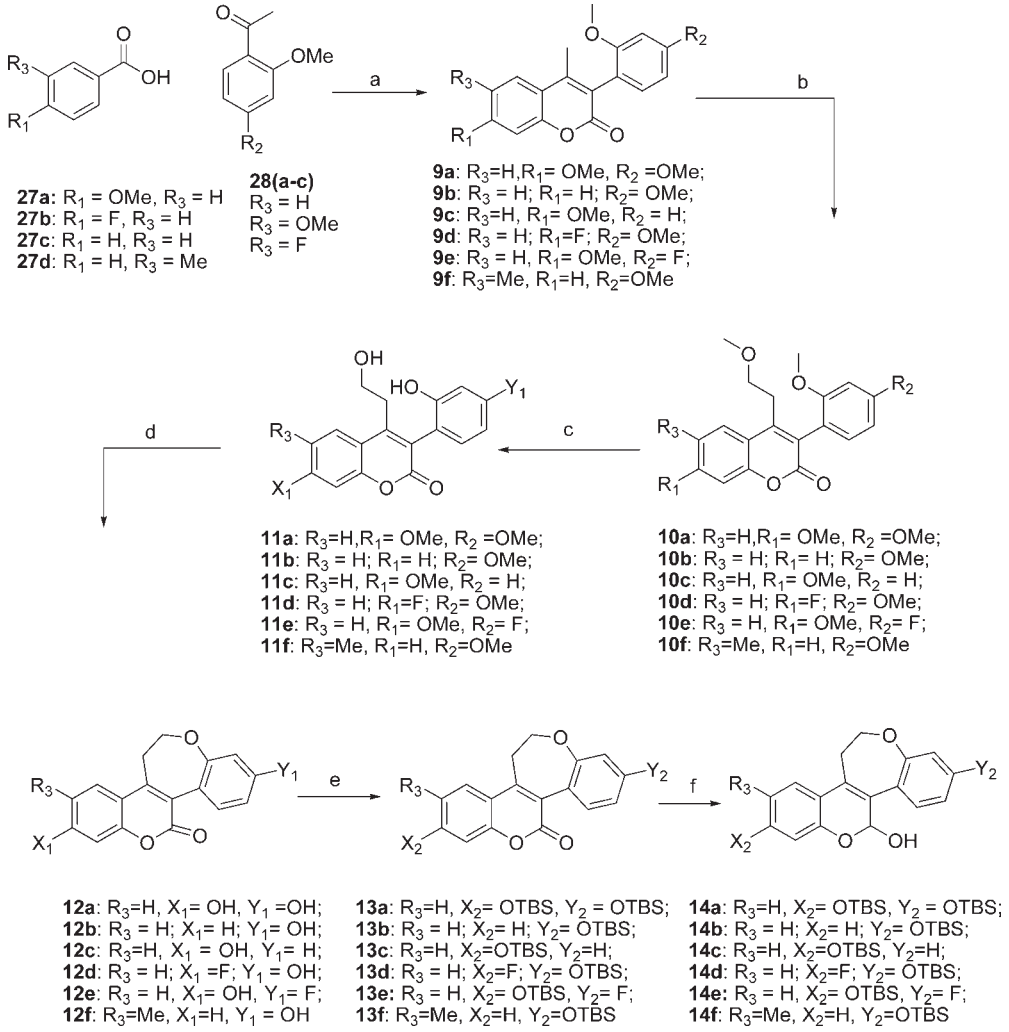


Figure 3. Design of seven- and eight-membered analogues.

Scheme 1. Synthesis of Key Lactal Intermediates[a]



[a] Reagent and reaction conditions: (a) Ac_2O, Et_3N, reflux, 36 h; (b) LiHMDS (1.5 equiv) MOMCl, THF, −30 to −10 °C; (c) BBr_3, CH_2Cl_2, room temp; (d) diethylazidodicarboxylate, DEAD, THF, PPh_3, room temp; (e) TBSCl, Et_3N, DCM, room temp; (f) DIBAL-H, toluene, DCM, −78 °C.

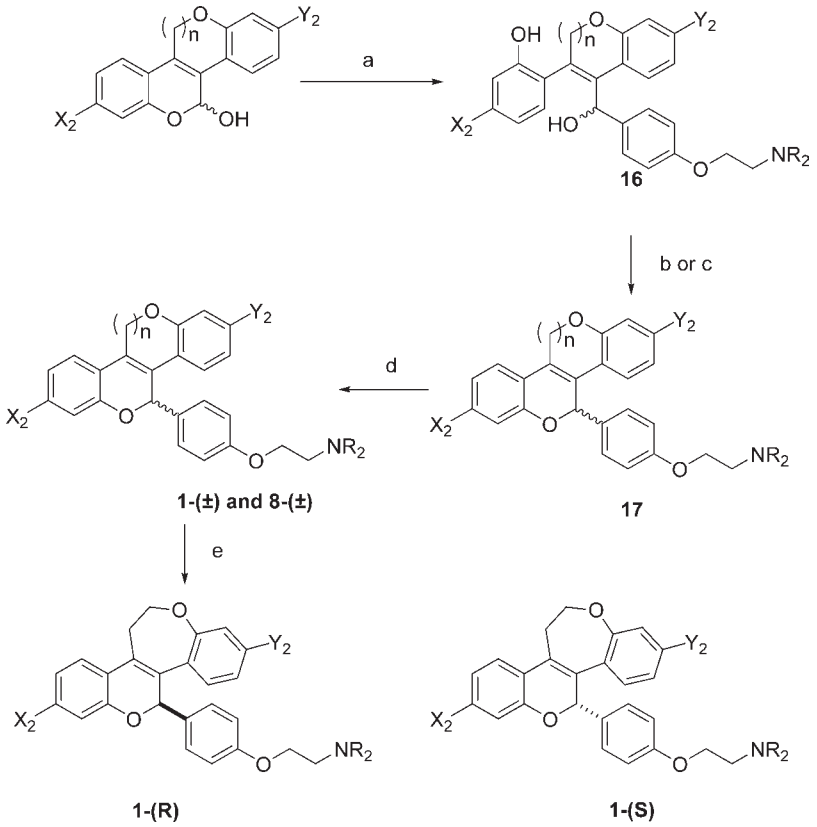
not show strong affinity to ERs in the in vitro binding assays (Figure 2).

To maintain certain conformation constrains for D-ring rotation while preventing oxidation from occurring, we decided to replace the $-CH_2O-$ linker in the C-ring of the bisbenzopyrans with a $-CH_2CH_2O-$ or $-CH_2CH_2CH_2O-$ linker to create the seven- and eight-membered ring derivatives as shown in Figure 3. We hoped that the change in planarity in C-ring would not affect the biological profile but prevent the formation of the oxonium intermediate associated with stability. Herein, we report new chromene-derived benzopyranobenzoxapane scaffold for SERMs. The synthesis, structure−activity relationships, and biological evaluations of these novel benzopyranobezooxapane (**II**) series are discussed.[8]

Chemistry. The basic tetracyclic ring system was synthesized using Perkin reaction followed by cyclization. In order to increase the throughput of the synthesis, several different routes were adopted to facilitate the introduction of the side chains. Most of the compounds were obtained in enantiomerically pure form by HPLC using ChiralPAK AD columns.[7i,8]

Synthesis of Tetracyclic Lactol 14. The preparation of fully functionalized benzopyranobenzoxapane system **14a** was achieved in four to five steps (Scheme 1). Modified Perkins reaction of a mixture of 2-hydroxyacetophenones **27** and

Scheme 2. Introduction of Side Chain[a]



[a] Reaction conditions: (a) **15** (ArMgx), THF, −78 °C; (b) conc HCl, toluene, 0 °C; (c) DEAD, Ph_3P, $^iPr_2NEt$, 0 °C; (d) TBAF, THF, 0 °C; (e) ChiralPAK AD column (^{i}PrOH was used as mobile phase).

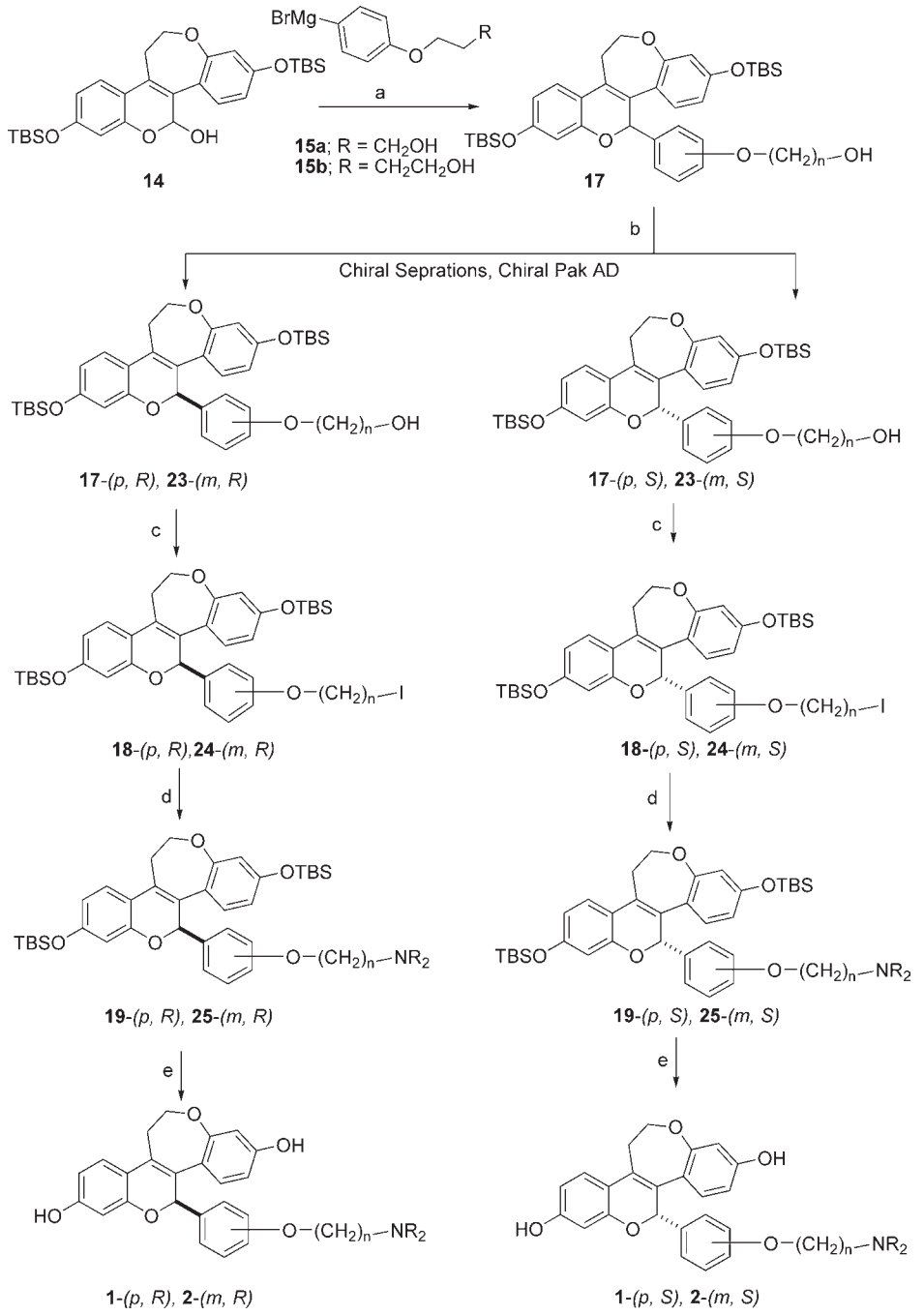
substituted phenylacetic acid **28** in the presence of triethylamine in refluxing acetic anhydride delivered coumarins **9a**−**f** in moderate to good yields. For the synthesis of benzopyranobenzoxapane **II** we needed one carbon homologation of **9**. When Li homoenolates of **9a**−**f** were reacted with MOMCl, MOM homologated products **10a**−**f** were obtained in good yields (67−81%). Global deprotection using BBr_3 in CH_2Cl_2 followed by cyclization under Mitsunobu protocol gave **12a**−**f** in 55−73% overall yields for two steps. The construction of the key tetracyclic intermediates was achieved in two steps: (i) capping the phenolic hydroxyl groups of **12** as *tert*-butyldimethylsilyl (TBDMS) derivatives **13a**−**f**; (ii) reduction with DIBAL-H to afford lactol **14a**−**f**.

General Synthesis of Benzopyranobenzoxapane (1). Benzopyranobenzoxapanes with various substitutions at ring A and ring B were synthesized as outlined in Scheme 2. The addition of Grignard reagent of the aminoalkoxyphenyl side chain **15** or the coresponding organolithio reagents to lactol **14** opened up the pyran ring B to afford the diol **16**, which recyclized to chromene **17** under Mitsunobu protocol or more conveniently by acid treatment (concentrated HCl) at low temperature in a hydrocarbon solvent such as toluene. The removal of mono- or di-TBS groups from **17** with tetrabutylammonium fluoride (TBAF) afforded the target compounds **1**-(±) in racemic form. The benzopyranobenzoxapane **1**-(±) was resolved using preparative HPLC with ChiralPAK AD column to yield optically pure compounds (*R*) and (*S*) with optical purity of more than 95% ee in all cases. The absolute stereochemistry was determined by single X-ray crystal structure analysis.[9]

Synthesis of Iodobenzopyranobenzoxapanes 18 and 24. In the synthesis of benzopyranobenzoxapane with various amine groups at para- or meta-substituted side chain, the iodo derivatives **18** and **24** served as the key intermediates. Grignard reagents **15a**,**b** were freshly prepared and were added to lactol to yield diols which upon treatment with concentrated HCl yielded the recyclized alcohols **17**-(±) and **23**-(±) in very good yields. The racemic mixtures of these alcohols were separated on chiral column AD and 20% IPA in hexanes as mobile phase to yield optically pure alcohol **17** or **23**-(*R*) or **17** or **23**-(*S*). The optically pure alcohol was reacted with PPh_3, imidazole, and iodine to yield the corresponding iodides **18** and **24**. By use of this protocol, large amount of these intermediates (5−10 g) could be readily synthesized. Various substituted secondary amines were reacted with iodide **18** or **24** in acetonitrile at 60 °C in the presence of anhydrous K_2CO_3 to yield various amino side chain substituted benzopyranobenzoxapanes **19** in good to moderate yields. Deprotection of TBS groups using TBAF yielded **1** in about 30−40% overall yield in optically pure form. The overall sequence is described in Scheme 3. This sequence was also used for the preparation of meta-substituted analogues **2**.

For synthesis of carboxylic acid and ester derivative **1l** and **1m**, a modified route was used as described in Scheme 4. For preparation of compound **1** (**l**−**o**) the corresponding alcohol was oxidized to the corresponding acid **1l**. This acid was treated with freshly prepared (in situ) diazomethane to yield the corresponding ester as described in Scheme 4 in good to moderate yields.

Scheme 3. Introduction of Various Amino Groups into the Side Chain[a]

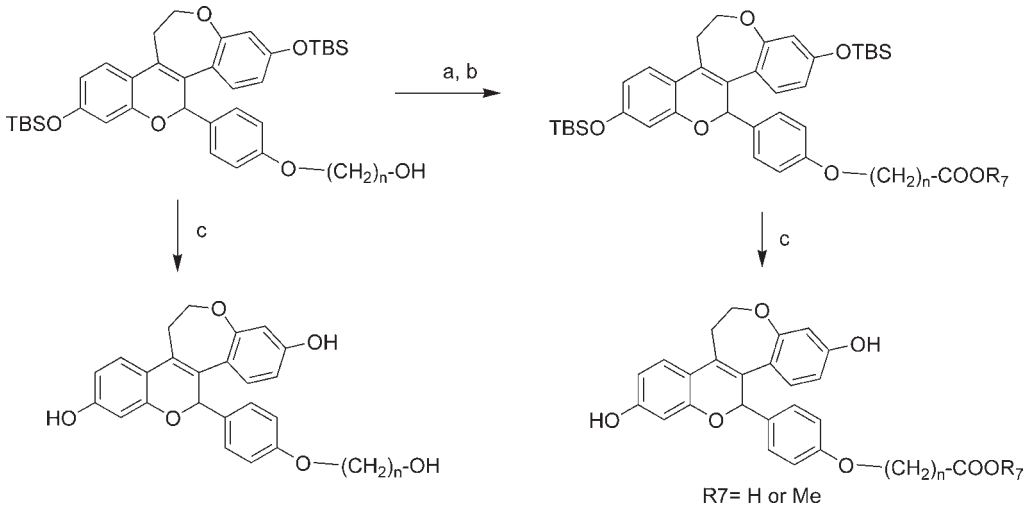


[a] Reagent and conditions: (a) THF, −20 °C; (b) chiral separation was done with 50 cm × 100 cm chiral PaKAD chiral coloum, ^{i}PrOH as mobile phase; (c) PPh_3, imidazole, I_2; (d) R_1R_2NH/DMF, heat at 60 °C; (e) TBAF, THF, 0 °C.

Synthesis of Methoxybenzopyranobenzoxapanes 4a−5a. The synthesis of dimethoxybenzopyranobenzoxapanes **7**-(*R*) and **7**-(*S*) was achieved in one step from the corresponding phenolic benzopyranobenzoxapanes **1a**-(*R*) and **1a**-(*S*), respectively, by methylation using excess of $TMSCHN_2$ in the presence of an excess of Et_3N in almost quantitative yield. Monomethoxybenzopyranobenzoxapanes **5**-(*R*), **6**-(*R*), **5**-(*S*), **6**-(*S*) were synthesized by generating a statistical mixture of the monomethoxy and dimethoxy derivatives with 1.5 equiv of $TMSCHN_2$. After separation of the dimethoxy derivative **7**, the regiomeric mixtures of these optically pure monomethoxy derivatives were separated on Chiral PAK AD using IPA as mobile phase. Using this protocol, it was possible to generate grams of **5**-(*R* or *S*) and **6**-(*R* or *S*) (Scheme 5).

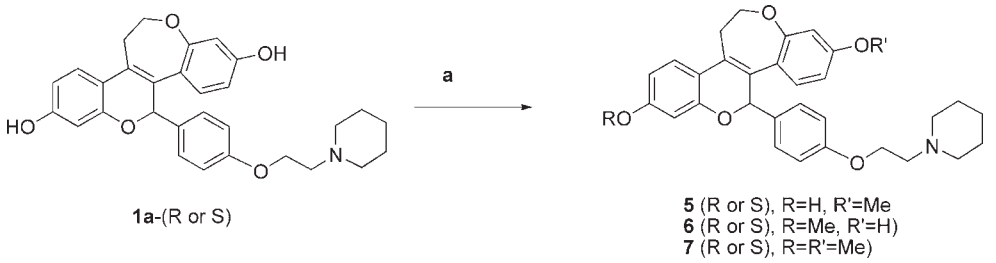
In Vitro and Immature Rat Uterotropic Assays. In Vitro Assay. Compounds were tested in four in vitro assays. New derivatives were screened in estrogen receptor β fluorescence polarization assay.[9] This assay monitors binding of a fluorescent analogue of estrogen (Fluormone ES2, Panvera) to the estrogen receptor. Plates are read in a fluorometer that can be set to polarization mode. A decrease in fluorescence relative to vehicle control is an indication of binding of a compound to the receptor.[10] At the same time all new derivatives were also tested for estrogen receptor α flash plate assay. This assay monitors binding of radiolabeled

Scheme 4. Hydroxy and Carboxylic Acid Derivatives[a]



[a] Reaction conditions: (a) Jones oxidation; (b) TMS-diazomethane; (c) TBAF, THF, 0 °C.

Scheme 5. Methoxy Derivatives[a]



[a] Reaction conditions: (a) $TMSCH_2N_2$ (1.5 equiv for **5** or **6** and 4.0 equiv for **7**), Et_3N (4 equiv).

estrogen to the estrogen receptor. It is performed on a BioMek 2000 (Beckman). Plates are read in a scintillation counter (Packard Top Count); decreased counts are an indication of binding of a compound to the receptor. The assay was run according to the procedure described by Allan et al.[10,11] The compounds were then evaluated for its activity in two cell-based functional assays, Ishikawa endometrial cell alkaline phosphatase assay, and MCF-7 breast cancer cell proliferation assay to determine the antagonist activity. The alkaline phosphatase assay in human endometrial Ishikawa cells was run according to the procedure described by Albert et al.[12] with minor modification. Ishikawa cells (from ATCC) were maintained in DMEM/F12 (1:1) phenol red free medium (Gibco) supplemented with 10% calf serum (Hyclone). Twenty-four hours prior to testing, the medium was changed to DMEM/F12 (1:1) phenol red free containing 2% calf serum. Compounds to be tested in the agonist mode were added to the culture media at varying concentrations. Compounds to be treated in the antagonist mode were prepared similarly, and 10 nM 17β-estradiol was also added to the culture media. The cells were then incubated at 37 °C for 3 days. On the fourth day, the media were removed, 1 volume of 1× dilution buffer (Clontech) was added to the well followed by addition of 1 volume of assay buffer (Clontech). The cells were then incubated at room temperature for 5 min. One volume of freshly prepared chemiluminescence buffer (1 volume of chemiluminescent substrate (CSPD) in 19 volumes of chemiluminescent enhancer with final concentration of CSPD at 1.25 mM; Sigma Chemical Co.) was added. The cells were incubated at room temperature for 10 min and then quantified on a luminometer. The increase of chemiluminescence over vehicle control was used to calculate the increase in alkaline phosphatase activity.

The MCF-7 cell proliferation assay was run according to the procedure described by Welshons, Taylor, and Jones[13] with minor modification. Briefly, MCF-7 cells (from Dr. C. Jordan, Northwestern University) were maintained in RPMI 1640 phenol red free medium (Gibco) in 10% FBS (Hyclone), supplemented with bovine insulin and nonessential amino acid (Sigma). The cells were initially treated with 4-hydoxyltamoxifen (10^{-8} M) and allowed to stand at 37 °C for 24 h. Following this incubation with tamoxifen, the cells were treated with compounds at various concentrations. Compounds to be tested in the agonist mode were added to the culture media at varying concentrations. Compounds to be treated in the antagonist mode were prepared similarly, and 10 nM 17β-estradiol was also added to the culture media. The cells were incubated for 24 h at 37 °C. Following this incubation, 0.1 μCi of ^{14}C-thymidine (56 mCi/mmol, Amersham) was added to the culture media and the cells were incubated for an additional 24 h at 37 °C. The cells were then washed twice with Hank's buffered salt solution (HBSS) (Gibco) and counted with a scintillation counter. The increase in the ^{14}C-thymidine in the compound treated cells relative to the vehicle control cells was reported as percent increase in cell proliferation.

Immature Rat Anti Uterotropic Studies. The compounds with SERM-like properties act as estrogen agonist or antagonist on uterus. It is well established that estrogens are

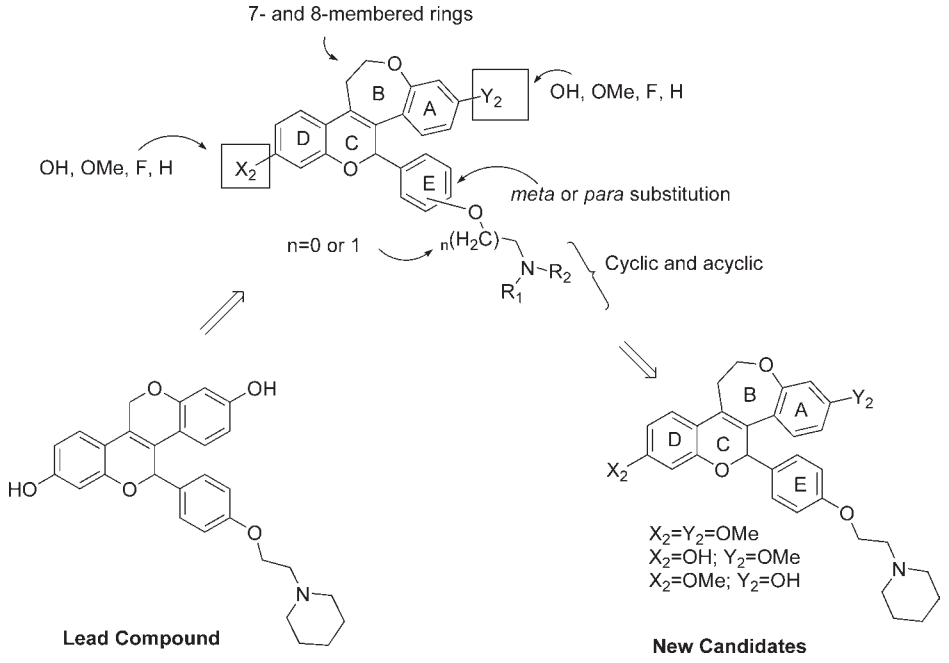
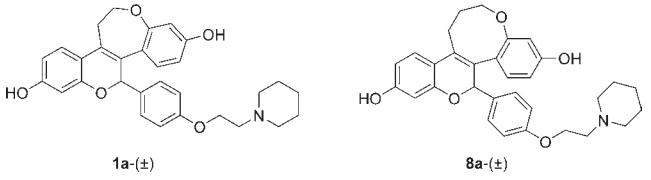


Figure 4. SAR studies and lead optimization.

Table 1. Comparison of Bisbenzopyran and Benzopyranobenzooxapane[a]



compd	ERα binding IC_{50} (nM)	ERβ binding IC_{50} (nM)	Ishikawa IC_{50} (nM)[b]	MCF-7 IC_{50} (nM)[c]	uterotropic activity inhibition (%)[d]
1a-(±)	13	31	8	19	77
8a-(±)	23	77	121	280	33

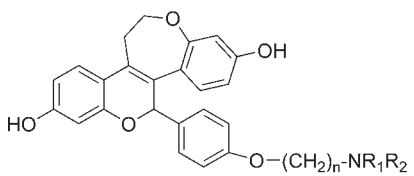
[a] All compounds were tested more than three times in these assays with high reproducibility. The average is shown here. [b] No agonist activity was found at 10 μM. [c] No agonist activity was found at 10 μM. [d] Inhibitions of estrone-stimulated uterine weight at 1 mg/kg.

known for their uterotropic activities to stimulate uterine growth. The immature rat uterotropic model is used to get a rapid and accurate assessment of the activity of a compound in the uterus. This can be used in either the agonist mode (compound alone) or antagonist mode (compound + estrogen). Because the animals have not matured sexually, there is minimal endogenous estrogen to complicate the evaluation. Immature rats that are unexposed to estrogen are administered with an estrogen, estrone, for 3 days. The uteri grow rapidly, and the weight of uterus increases sharply in 3 days. Co-treatment with estrogen antagonist could block the stimulation, while estrogen agonist synergistically enhances the stimulation. The difference between the weight of uterus from vehicle control animals and that from treated animals is a sensitive indicator of estrogen agonist or antagonist activity. This model has been used as a classical measure to evaluate activities of estrogen agonists and antagonists including SERMs. The effects of these compounds in this model have been predictive of the clinical responses reported in women[18]. In the agonist mode and antagonist mode, the test compounds were administered orally once daily (1 mg/kg) for 3 days and the effect on uterine wet weight was compared with vehicle, estrone, tamoxifen, and raloxifene.[13−15]

Structure−Activity Relationships. The overall effort for SAR studies is summarized in Figure 4. The representative seven- and eight-membered derivatives **1a**-(±) and **8a**-(±) (Table 1) exhibited excellent chemical stability which further confirmed our hypothesis for the instability of the bisbenzopyran analogues. Both compounds were evaluated in in vitro assays for their estrogenic and antiestrogenic activity. The binding affinities of **1a**-(±) and **8a**-(±) for ERs were compared to the initial lead compounds. On the basis of the MCF-7 and Ishikawa cell based functional data, compound **8a**-(±) seemed to have lost about 10- to 20-fold of antagonist activity [**8a**-(±) vs **1a**-(±)]. In immature uterotropic assays, compound **1a**-(±) had significantly higher antiuterotropic inhibition compared to **8**-(±). On the basis of favorable data for **1a**-(±), the racemic compound was resolved and then evaluated in ERs binding affinity as well as for antagonist potency in both Ishikawa and MCF-7 cell based functional assay. Enantiomer **1a**-(*R*) was about 10-fold more potent than **1a**-(*S*) in both binding and functional assays. In antiuterotropic assay, both compounds showed inhibitory activity. The antiuterotrpic activity of **1a**-(*R*) was significantly higher than that of **1a**-(*S*) (Table 2).

To examine the SAR of the basic side chain, various tertiary amino groups were incorporated. Replacing piperidine

Table 2. In Vitro and in Vivo Characterizations of Benzopyranobenzoxapane[a]



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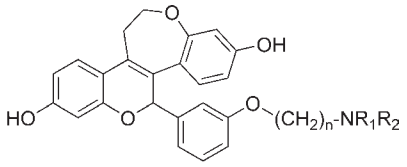


B

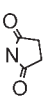
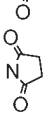
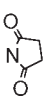
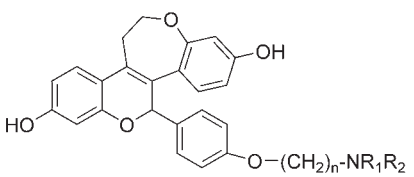
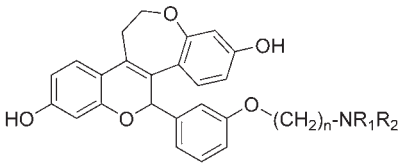
Entry	Cpd	Form	n	NR_1R_2	ERα Binding IC_{50} (nM)	ERβ Binding IC_{50} (nM)	Ishikawa IC_{50} (nM)[b]	MCF-7 IC_{50} (nM)[c]	Uterotropic activity Inhibition (%)[d, e]
1	**1a**-(*R*)	**A**	2		1.1	21	0.20	11	135
2	**1a**-(*S*)	**A**	2		3.4	16	32	174	88
3	**1b**-(*R*)	**A**	2	NMe_2	3.3	23	61	293	25
4	**1b**-(*S*)	**A**	2	NMe_2	11	12	405	687	0 (100)[f]
5	**1c**-(*R*)	**A**	2	N^iPr_2	5.4	20	287	220	30
6	**1c**-(*S*)	**A**	2	N^iPr_2	5.6	18.5	35	424	30(80)[f]
7	**1d**-(*R*)	**A**	2		2.2	19	41	217	60
8	**1d**-(*S*)	**A**	2		2.4	13.4	128	401	50
9	**1e**-(*R*)	**A**	2		1.2	14	10	150	10
10	**1e**-(*S*)	**A**	2		2.5	8.7	165	688	20
11	**1f**-(*R*)	**A**	2		1.6	35	43	816	40
12	**1f**-(*S*)	**A**	2		10	11	>10000	>10000	0
14	**1g**-(*R*)	**A**	2		1.2	27	87	2460	85
15	**1g**-(*S*)	**A**	2		111	390	>10000	>10000	0
16	**1h**-(*R*)	**A**	2		8.7	86	90	1550	30
17	**1h**-(*S*)	**A**	2		312	580	>10000	>10000	5
19	**1i**-(*R*)	**A**	2		4.8	0.64	>10000	>10000	0
20	**1i**-(*S*)	**A**	2		6.2	18.6	>10000	>10000	0
21	**1j**-(*R*)	**A**	3		2.63	12.7	>10000	>1000	0
22	**1j**-(*S*)	**A**	3		40.97	5.68	>10000	>10000	0

Table 2. Continued



A



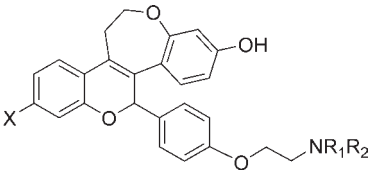
B

Entry	Cpd	Form	n	NR_1R_2	ERα Binding IC_{50} (nM)	ERβ Binding IC_{50} (nM)	Ishikawa IC_{50} (nM)[b]	MCF-7 IC_{50} (nM)[c]	Uterotropic activity Inhibition (%)[d, e]
23	**1k**	**A**	2	OH	310	11	>10000	>10000	0
24	**1l**	**A**	3	OH	326	44	>10000	>10000	0
25	**1m**	**A**	1	COOMe	4.8	16	>10000	>10000	0
26	**1n**	**A**	1	COOMe	8.9	16	>10000	>10000	0
27	**1o**-(*R*)	**A**	2	COOH	120	250	>10000	>10000	0
28	**1o**-(*S*)	**A**	2	COOH	580	44	>10000	>10000	0
29	**1p**-(*R*)	**A**	3		22	31	420	1200	23
30	**1p**-(*S*)	**A**	3		55	19	590	1800	15
31	**2a**-(*R*)	**B**	2		150	380	>10000	>10000	0
32	**2a**-(*S*)	**B**	2		190	200	>10000	>10000	0
33	**2b**-(*R*)	**B**	2		>1000	>1000	>10000	>10000	NA[g]
34	**2b**-(*S*)	**B**	2		>1000	>1000	>10000	>10000	NA[g]
35	**2c**-(*R*)	**B**	2		>1000	>1000	>10000	>10000	NA[g]
36	**2c**-(*S*)	**B**	2		>1000	>1000	>10000	>10000	NA[g]
37	RAL				1.8	8.2	24	222	105
38	TAM				nd[g]	nd[g]	nd[g]	nd[g]	0(109)[f]

[a] All compounds were tested more than three times in these assays with high reproducibility. The average is shown here. [b] No agonist activity was found at 10 μM. [c] No agonist activity was found at 10 μM. [d] Inhibitions of estrone-stimulated uterine weight at 1 mg/kg. [e] In these uterotopic assays, when compounds, or raloxifene, were administered alone, they showed no significant agonistic activity to stimulate uterine growth except compounds **1b**-(*R* or *S*), and these effects were similar to E2 and TAM which is a significant increase in the uterine wet weight ($P < 0.005$). [f] Stimulation in % shown in parentheses. [g] Not determined.

by *N*,*N*-dimethylamine or *N*,*N*-diisopropylamine did not alter the binding affinity for ERs but decreased the potency in MCF-7 and Ishikawa cell based functional assays (**1b** and **1c** vs **1a**, Table 2). These compounds also showed poor antiuterotropic inhibitory activity when tested in antagonist mode. Interestingly, **1b**-(*S*) and **1c**-(*S*) in uterotropic assays showed strong stimulatory activity similar to that of tamoxifen (Table 2, entries 4 and 6). In cases where piperidine was replaced by pyrolidine or azapine (**1d** or **1f**), almost all ER binding affinity was retained while antagonist potency decreased slightly in Ishikawa and MCF-7 cell based functional assays. The strong inhibitory effect in antiuterotrpic assay was observed for **1d**-(*R*) and **1d**-(*S*). Both enantiomers of **1f** showed poor inhibitory effects in antiuterotropic assay. When piperidine ring was replaced by other heterocyclic rings, such as morpholine and 1-methylpiperazine, the antagonist potency in Ishikawa and MCF-7 cell based functional assays was almost abolished (**1f**, **1 h** vs **1a**, Table 2).

Table 3. In Vitro and in Vivo Characterization of Benzopyranobenzoxapane[a]



Entry	Cpd	X	NR_1R_2	ERα Binding IC_{50} (nM)	ERβ Binding IC_{50} (nM)	Ishikawa Antag. IC_{50} (nM)[b]	MCF-7 Antag. IC_{50} (nM)[c]	Uterotropic activity Inhibition (%)[d,e]
1	**3a**-(*R*)	H	NMe_2	16	105	134	1350	55
2	**3a**-(*S*)	H	NMe_2	13	23	194	1456	18 (70% stimul.)[f]
3	**3b**-(*R*)	H	NEt_2	5	108	113	1570	80
4	**3b**-(*S*)	H	NEt_2	9	28	133	1660	30 (100% stimul.)[f]
5	**3c**-(*R*)	H		11	125	293	>10000	110
6	**3c**-(*S*)	H		4.5	22	68	1920	28
7	**3d**-(*R*)	H		5.8	99	76	1210	130
8	**3d**-(*S*)	H		4.2	24	150	1236	20
9	**3e**-(*R*)	F	NEt_2	5	108	113	1570	80
10	**3e**-(*S*)	F	NEt_2	7	11	122	1200	11
11	**3f**-(*R*)	F		3.3	66	81	1300	22
12	**3f**-(*S*)	F		5	31	161	1355	33

[a] All compounds were tested more than three times in these assays with high reproducibility. The average is shown here. [b] No agonist activity was found at 10 μM. [c] No agonist activity was found at 10 μM. [d] Inhibitions of estrone-stimulated uterine weight at 1 mg/kg. [e] In these uterotopic assays, when compounds, or raloxifene, were administered alone, they showed no significant agonistic activity to stimulate uterine growth except compounds **3a**-(*S*) and **3b**-(*S*), and these effects were similar to E2 and TAM which is a significant increase in the uterine wet weight ($P < 0.005$). [f] Stimulation in % shown in parentheses.

These compounds also had poor inhibitory effects in antiuterotrpic assay. Compound **1g**-(*R*), where the side chain contains thiomorpholine, showed very strong inhibitory affect in antiuterotropic assay. We also replaced the side chain piperidine by a neutral or acidic group that bears hydrogen bonding acceptors or donors such as pyrrolidine-2,5-dione, hydroxyl, −COOH, and −COOMe. Such modifications retained most of the binding affinity but had no antagonist potency in Ishikawa or MCF cell based functional assays.

The length of alkoxy group, $OCH_2CH_2-NR_2$ attached to E-ring was also extended to one more carbon atom ($-OCH_2-CH_2CH_2-NR_2$) to give **1p**-(*R*) as well as **1p**-(*S*); both had good binding affinity but lost about 100-fold potency in Ishikawa cell based functional assays. Both compounds had $IC_{50} > 1$ μM in MCF-7 cell based functional assays.

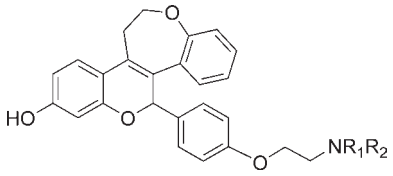
The alkoxy group attached to E-ring was moved to meta position. Both **2a**-(*R*) and **2a**-(*S*) had diminished binding affinity and lost all antagonist potency in MCF-7 and Ishikawa cell based function assays. All estrogenic activity was lost when piperidine was replaced by other heterocyclic rings (**2b** and **2c** vs **2a**, Table 2, entries 29−34).

Table 3 shows the SAR for derivatives where the hydroxy group in A-ring is either replaced by H or F. Compound **3d**-(*R*) was comparable to that of **1a**-(*R*) in ER binding affinity, antagonist potency in MCF-7 and Ishikawa based functional assays, and inhibitory potency in antiuterotropic assay. Interestingly, strong stimulatory effect was observed for compounds **3a**-(*S*) and **3b**-(*S*) where the side chain piperidine was replaced by NMe_2 and NEt_2. However, the enantiomers of this compound, **3a**-(*R*) and **3a**-(*R*), had strong inhibitory potency in antiuterotropic assays. When hydroxy group in D-ring was replaced by fluorine atom, the resulting compounds [**3e**-(*R*) and -(*S*) and **3f**-(*R*) and -(*S*)] had good profiles in in vitro assays but weak inhibitory activity in antiuterotropic assays. Compound **3e**-(S) showed no stimulatory response in antiuterotropic assay. [**3e**-(*S*) vs **3b**-(*S*)].

In Table 4, the SAR was related to D-ring deshydroxy derivatives. In these cases (*R*) optical isomers of **4a**, **4b**, and **4c** have about 10-fold better affinity toward ERs. Irrespective of the side chain, all compounds were weak inhibitors in antiuterotropic assay.

Compounds **1a**-(*R*) and **1a**-(*S*) were converted to dimethoxy derivatives **7**-(*S*) and **7**-(*R*) as shown in Scheme 5. Compound **7**-(*S*) had no binding affinity for either ERα or ERβ receptor. In antiuterotropic assay, poor inhibitory

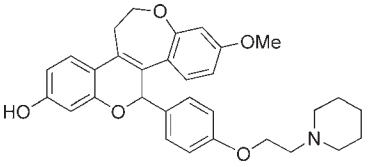
Table 4. In Vitro and In Vivo Characterization of Benzopyranobenzoxapanes[a]



Entry	Cpd	NR_1R_2	ERα Binding IC_{50} (nM)	ERβ Binding IC_{50} (nM)	Ishikawa Antag. IC_{50} (nM)[b]	MCF-7 Antag. IC_{50} (nM)[c]	Uterotropic activity Inhibition (%)[d]
1	**4a**-(*R*)	NMe_2	180	205	8990	>10000	23
2	**4a**-(*S*)	NMe_2	11.1	30	158	1350	20
3	**4b**-(*S*)		4	41	144	1844	7
4	**4b**-(*R*)		85	140	2670	10000	11
5	**4c**-(*R*)		100	200	259	10	5
6	**4c**-(*S*)		6.3	63	25.9	150	12

[a] All compounds were tested more than three times in these assays with high reproducibility. The average is shown here. [b] No agonist activity was found at 10 μM. [c] No agonist activity was found at 10 μM. [d] Inhibitions of estrone-stimulated uterine weight at 1 mg/kg.

Table 5. In Vitro and in Vivo Characterization of Benzopyranobenzoxapanes[a]



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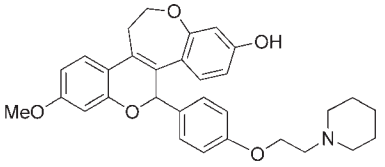

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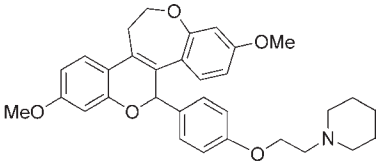
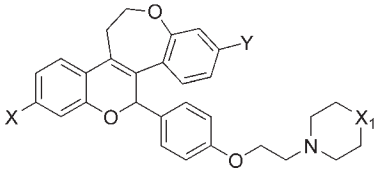


7

entry	compd	ERα binding IC_{50} (nM)	ERβ binding IC_{50} (nM)	Ishikawa antag IC_{50} (nM)[b]	MCF-7 antag IC_{50} (nM)[c]	uterotropic activity inhibition (%)[d]
1	**5**-(*R*)	5.8	99	76	1210	130
2	**5**-(*S*)	4.2	24	150	1236	20
3	**6**-(*R*)	9	7	259	10	99
4	**6**-(*S*)	6.3	63	25.9	150	12
5	**7**-(*R*)	64	NA	1736	> 10000	121
6	**7**-(*S*)	> 10000	> 10000	> 10000	> 10000	7

[a] All compounds were tested more than three times in these assays with high reproducibility. The average is shown here. [b] No agonist activity was found at 10 μM. [c] No agonist activity was found at 10 μM. [d] Inhibitions of estrone-stimulated uterine weight at 1 mg/kg.

Table 6. Single Dose Pharmacokinetics Profiles of SERMs[a]



1a -(*R*); X= OH, Y= OH; X_1= CH_2
1g-(*R*); X= OH, Y= OH; X_1= S
4c-(*R*); X= OH, Y= H; X_1= CH_2
5-(*R*); X= OH, Y= OMe; X_1= CH_2
6-(*R*); X= OMe, Y= OH; X_1= CH_2
7-(*R*); X= OMe, Y= OMe; X_1= CH_2

PK parameter (po)	**1a**-(*R*)	**1g**-(*R*)	**4c**-(*R*)	**7**-(*R*)	**6**-(*R*)	**5**-(*R*)
F_{po} (%)	11	9	9	30	58	61
C_{max} (ng/mL)	91	89	30	168 + metabolites (**5** + **6** + **1a**)-(*R*) = 130	219 + metabolite **1a**-(*R*) = 12	228 + metabolite **1a**-(*R*) = 14
T_{max} (h)	5	4.8	4.8	5	6	6
$T_{1/2}$ (h)	4.8	5.28	5.28	7.2	19.8	18.6
AUC (ng·h/mL)	1011	1528	1128	2268	6918	6734

[a] These compounds were formulated for oral dosing as a uniform suspension in 0.5% methylcellulose vehicle.

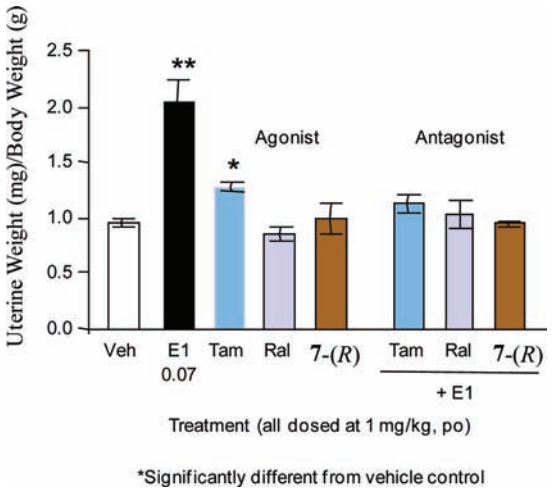


Figure 5. Effect of **7**-(*R*) on the uterine weight in immature rats.

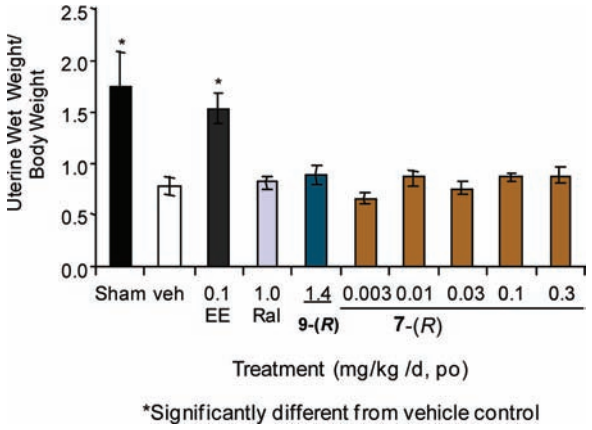


Figure 6. Rat 6-week osteopenia model: effect of **7**-(*R*) on uterine wet weight.

activity was observed. On the other hand, **7**-(*R*) had an IC_{50} in ERα of about 64 nM but no activity in ERβ receptor (>100 μM). A strong inhibitory activity was observed for **7**-(*R*) in the antiuterotropic assay. Compounds **1a**-(*R*) and **1a**-(*S*) were also converted into corresponding monomethoxy derivatives **5**-(*R*) and **6**-(*R*) or **5**-(*S*) and **6**-(*S*) as shown in the Scheme 5. Both *R* and *S* derivatives of these monomethoxy derivatives had good profile in the in vitro assays. However, only **5**-(*R*) and **6**-(*R*) showed strong inhibitory activity in the uterotropic assay (Table 5).

In general, compounds with absolute configuration (*R*) are significantly more potent in antiuterotropic assays. Piperidine, thiomorpholine, and azepane are among the best side chain functional groups for antagonist potency in Ishikawa and MCF-7 cell based functional assays. Replacement of piperideine ring system by dialkyamine, like $-NMe_2$, $-NEt_2$, or $^iPr_2N-$, resulted in strong stimulatory activity in antiuterotropic assays. Consistent with literature observations, $-OCH_2CH_2NR_2$ is the optimal side chain attached to para position to the aromatic ring. The basic amine is essential for the antagonist potency in MCF-7 and Ishikawa based functional assays. At least one hydroxy group in A ring or D ring is required for binding affinity for ERs. Compound **1a**-(*R*) and its methoxy derivatives, attached to either A ring or D ring **5**-(*R*) or **6**-(*R*) or dimethoxy derivative **7**-(*R*) demonstrated excellent profiles

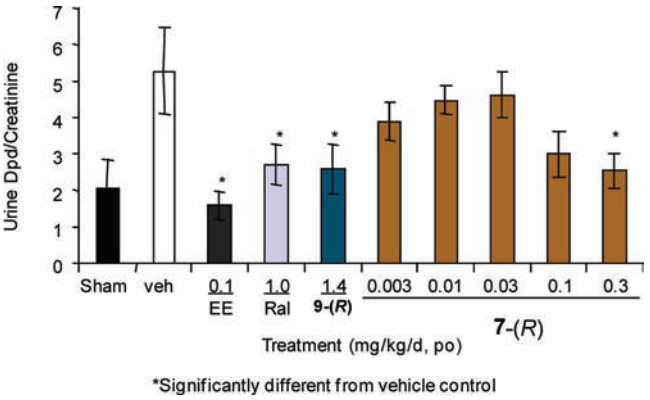


Figure 7. The 6-week osteopenia model: effect of **7**-(*R*) on urine Dpd.

in in vitro assays as well in antiuterotropic assays and was selected as a candidate for in depth evaluations.

Pharmacokinetic Results. On the basis of estrogen receptor (ERα and ERβ) binding affinity, antiestrogenic potency in MCF-7 and Ishikawa cell-based functional assays, and inhibitory activity in the uterotropic assay, the lead compounds were selected for evaluation of their pharmacokinetic parameters in rats. For pharmacokinetic studies, rats were dosed intravenously (iv) at doses of 1−3 mg/kg and by oral gavage at a dose of 10 mg/kg with compounds **1**−**4**. Compounds were formulated for iv dosing as a solution in 10% β-cyclodextrin, and these compounds were typically formulated for oral dosing as a uniform suspension in 0.5% methylcellulose vehicle. Blood samples (0.5 mL) were collected into heparinized tubes postdose via orbital sinus puncture. Blood samples were centrifuged for cell removal, and 200 μL of plasma supernatant was transferred to a clean vial. The plasma samples were prepared in acetonitrile along with an internal control, analysis was carried out by LC−MS−MS along with standards, and then pharmacokinetic parameters were assessed. The pharmacokinetic profiles of compounds **1**−**4**, **12**, and **13** are summarized in Table 6.[9b]

Compounds **1a**-(*R*), **1g**-(*R*), and **4c**-(*R*) had poor overall bioavailability and low exposure to tissues. The moderate clearance rate indicates that the poor bioavailability may have been due to poor absorption of these compounds. The zwitterionic form of the compounds may have further hampered the absorption. Therefore, we decided to cap the hydroxy group with a methyl group. We were pleased to observe that compound **7**-(*R*) had good overall bioavailability (F_{po} = 30%) with moderate exposure and half-life. We were also pleased to observe that when **7**-(*R*) was administered orally, the potent anti-estrogenic metabolites **5**-(*R*) and **6**-(*R*) were formed along with a small amount of **1a**-(*R*). The total maximum concentration of these compounds almost reached 135 ng/mL. When metabolites **5**-(*R*) and **6**-(*R*) were dosed in pharmacokinetic studies, both metabolites had excellent bioavailability (F_{po} = 58% for **6**-(*R*) and F_{po} = 61% for **5**-(*R*)). The overall bioavailability of compound **1a** was only 6% with very low exposure. Part of the reason for the high bioavailabiilty of monomethoxy derivatives **5**-**6**-(*R*) could be electron donating methoxy groups, which reduce the acidity of the phenolic group, thereby weakening the zwitterion and improving the absorption.[9b]

Pharmacological Results. Recently, we reported that our phase 2 clinical compound **9**-(*R*) possessed a unique

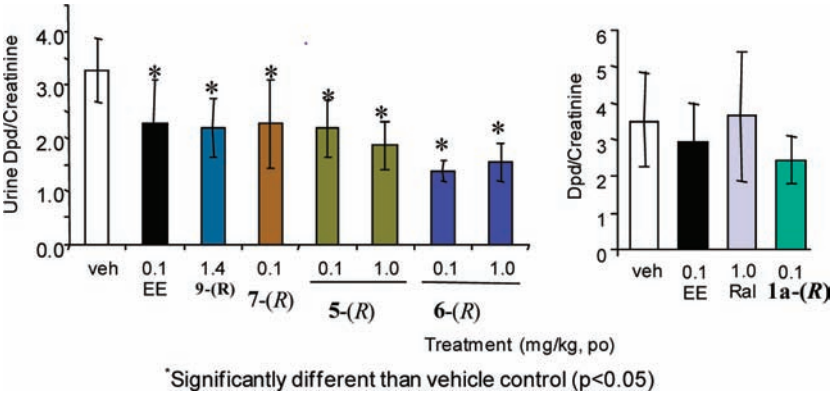


Figure 8. Effect of 2 weeks of treatment with metabolites of **7**-(*R*) on bone turnover as assessed by urine Dpd.

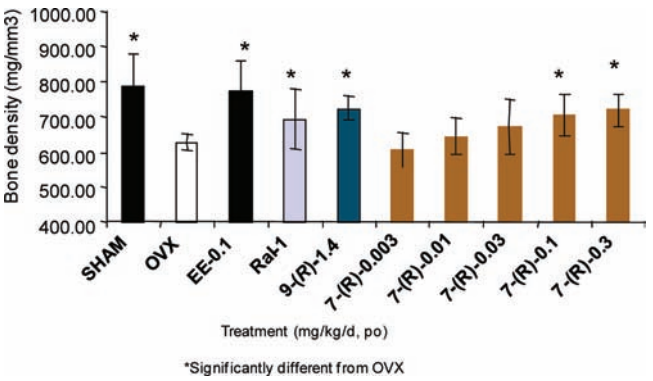


Figure 9. Effect of **7**-(*R*) on total bone density (tibia, 6 weeks).

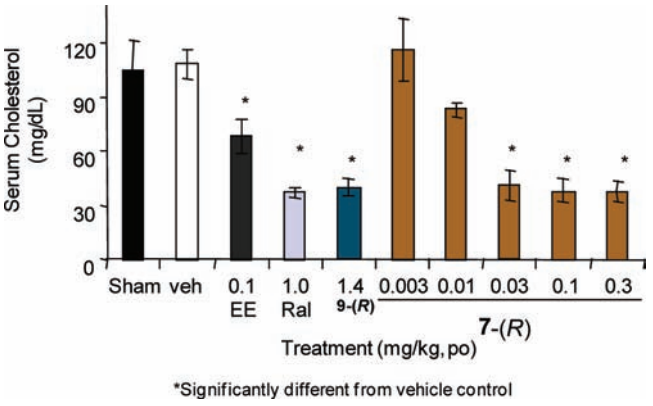


Figure 10. The 6-week osteopenia model: effect of **7**-(*R*) on serum cholesterol.

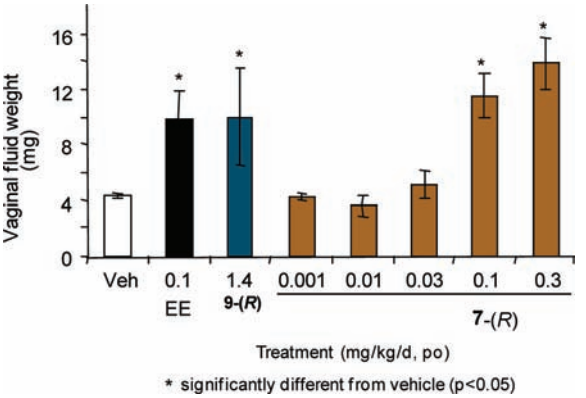


Figure 11. The 2-week adult OVX rat model: effect of **7**-(*R*) on vaginal fluidity.

pharmacological profile as a SERM with a potential for reduced hot flush and vaginal dryness and an antagonist effect in breast tissue while maintaining the beneficial effects of the marketed SERMs raloxifene and tamoxifene.[7a] Compound **9** had a shortcoming in that it was a prodrug; the active metabolite was unstable under ambient conditions. On the basis of an in vivo, anti-estrogenic assay (for **7**-(*R*), see Figure 5) and pharmacokinetic data, compound **7**-(*R*) was evaluated further in several in vivo models of estrogen activity. The metabolites **1a**-(*R*), **5**-(*R*), and **6**-(*R*) were also evaluated in some of the studiese. These models were used to assess the tissue selective activity of the compounds. In these studies, all compounds were orally administered to animals in an aqueous homogeneous suspension (in 0.5% Methocel) once daily for the appropriate treatment time. For the hot flush assay, sesame oil was used as the vehicle. In all cases, the compound was administered as a suspension. The biological outcome was compared with two standards, our own development compound **9**-(*R*) and raloxifene.[7a,14−17]

Adult Ovariectomized Rat Models. The adult ovariectomized estrogen-deficient rat model was applied to evaluate the tissue selective effects of SERMs. The model is useful because simultaneous responses in several tissues can be evaluated. It provided information on ovariectomy-induced bone loss, plasma lipid levels, and uterine and vaginal effects, as well as other pathological changes in the cardiovascular and reproductive systems. The model was used to characterize estrogen agonist and antagonist activities of **7**-(*R*). Treatment of test compounds was continued for 2−6 weeks. Bone density measurements on isolated bones were conducted in the 6-week model. The effects of these compounds in this model were in line with the clinical responses in reported women.[15−17] Adult female animals (> 6 months old, Charles River Laboratories, Wilmington, MA) were used. The rats were housed individually in wire-mesh cages at an ambient temperature of 21−23 °C with an automated 12 h light/dark cycle and access to water and a commercial rodent food ad libitum [we used a casein-based diet to reduce food-borne estrogens]. Each treatment group consisted of 6−14 animals. The animals were ovariectomized under sterile conditions and anesthesia. Twenty-four hours after surgery, compound **7**-(*R*) or metabolites **1a**-(*R*), **5**-(*R*), **6**-(*R*) were administered daily by oral gavage for 2 or 6 weeks. Other reference treatment groups included sham-operated control, ovariectomized controls, and ethynylestradiol treated (EE, 5 (mg/kg)/day) and raloxifene treated (1 (mg/kg)/day)

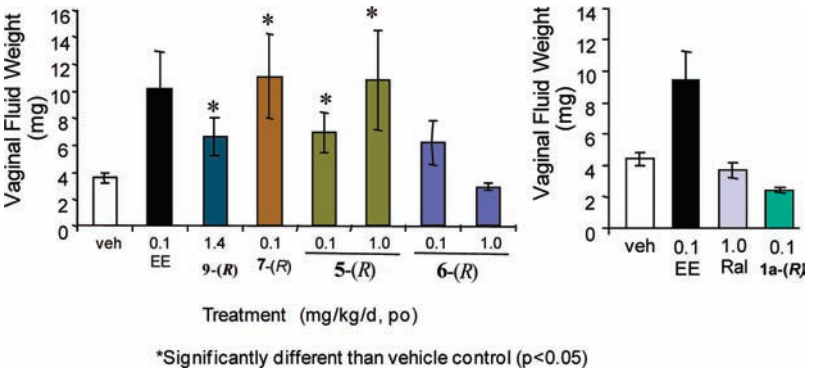


Figure 12. The 2-week adult OVX rat model: effect of **5**-(*R*) and 6-(*R*) vaginal fluidity.

groups. Methocel (0.5%) was used as the vehicle for all compounds including compound **9**-(*R*).

Measurement of Uterine Weight and Uterine Epithelial Thicknesses. In the above model, animals were euthanized at the end of the study with CO_2. The uteri were excised, cleaned of surrounding fat and connective tissue, incised slightly to release luminal fluid, blotted on filter paper, and weighed until constant weight. **7**-(*R*) showed modest, dose dependent effects on uterine weight when administered alone. The magnitude of this response was comparable to that seen with **9**-(*R*) and was not significantly different from raloxifene. In a separate study, the metabolites **5**-(*R*) and **6**-(*R*) as well as **1a**-(*R*) had little or no agonist activity in the uterus of adult ovariectomized rats following 2 weeks of treatment. There was no significant difference in uterine wet weight in rats treated with either metabolite compared to those from vehicle treated animals (Figure 6). Similar effects are well documented with raloxifene.[16]

After the uterine tissue was weighed, it was fixed in formalin to prepare it for immunohistochemical analysis and the uterine epithelial thickness was measured as described by Clark et al.[15a,15b] The uterine epithelial thicknesses is a very sensitive gauge of estrogenic activity in uterous.[15] The activity in this model was compared to that of **9**-(*R*) and raloxifene (Figure 14).

Histomorphometric measurement of rat uterine epithelium showed that estrone, known to induce endometrial hyperplasia and neoplasm, stimulated epithelium proliferation and caused increase of epithelial thickness after 6 weeks of treatment. The epithelial thickness in rats treated with estrone at 0.1 (mg/kg)/day was significantly higher than those from all other treatment groups ($p < 0.05$). The effect of **7**-(*R*) on the epithelium was similar to that of raloxifene. That is, there was a minor increase in epithelial thickness in animals treated with raloxifene (1 (mg/kg)/day) and **7**-(*R*) (at 0.001, 0.03, and 0.3 (mg/kg)/day). No difference was found between raloxifene at 1 (mg/kg)/day and **7**-(*R*) at all doses. There was also no difference between **7**-(*R*) at the three doses. These results along with uterine weight suggest that that compound **7**-(*R*) does not stimulate uterine tissue. (Figure 14). Similar observations were also found for compounds **5**-(*R*) and **6**-(*R*).[9b]

Bone Turnover. Urine deoxypyridinoline (Dpd) is a sensitive biomarker for bone resorption. Ovariectomy in female rats causes depletion of endogenous estrogen, which leads to an increase in bone resorption. This subsequently causes bone loss, which mimics the situation in postmenopausal women. In this model, urine Dpd increased significantly in OVX ovariectomized control animals compared to sham

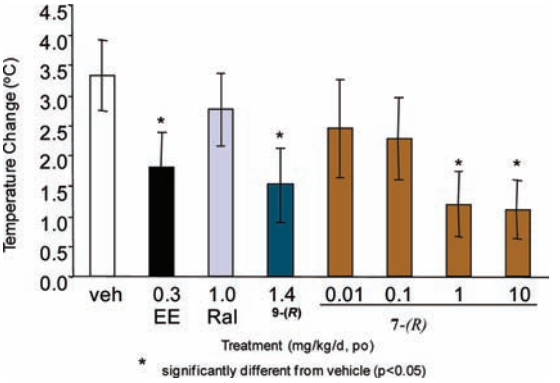


Figure 13. Effect of **7**-(*R*) on rat hot flush model.

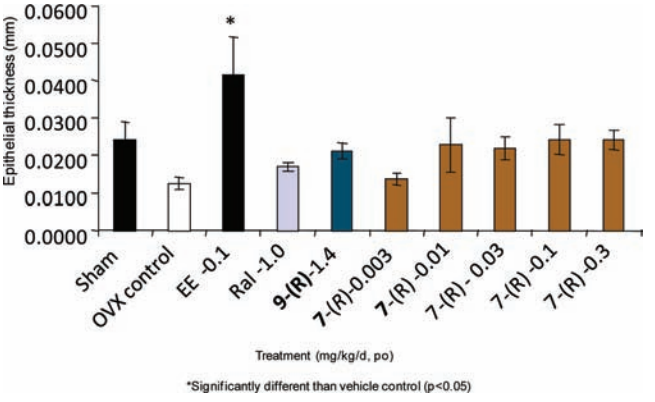


Figure 14. Effect of **7**-(*R*) on uterine epithelial thickness after 6 weeks of treatment.

operated animals after 2 weeks of treatment (Figure 7).[17] Compound **9**-(*R*) (1.4 mg/kg) and raloxifene suppressed the urine Dpd level as expected. All other parameters in these animals responded as predicted to EE treatment. **7**-(*R*) was very potent in its ability to lower urine Dpd levels. The effect was statistically significant at a dose of 0.3 mg/kg, and a trend toward decreased Dpd levels at lower doses for lowering of urine Dpd levels was also found. The metabolites **5**-(*R*), **6**-(*R*), and **1a**-(*R*) were effective at lowering bone turnover, as measured by urine Dpd levels, in rats following 2 weeks of treatment (Figure 8). In general, **7**-(*R*) was more potent than its metabolite **5**-(*R*) and **6**-(*R*). On the basis of the effect of **7**-(*R*) on Dpd levels, bone mineral density was also measured for **7**-(*R*). For the measurement of bone mineral density, the left tibia was removed from the animal, cleaned, and fixed in 10% formalin. Ex vivo peripheral quantitative

Table 7. Summary of in Vivo Efficacy Studies for **7**-(*R*)

	7-(*R*)	**9**-(*R*)	ethinyl estradiol	raloxifene
immature rat uterotropic test	antagonist	antagonist	agonist	antagonist
result for adult ovariectomized rat model				
uterus	antagonist	antagonist	agonist	antagonist
serum cholesterol	agonist	agonist	agonist	agonist
bone	agonist	agonist	agonist	agonist
hot flush	agonist	agonist	agonist	antagonist
vagina	agonist	agonist	agonist	antagonist

computerized tomography (pQCT) was conducted, and trabecular and cortical bone mineral density and bone mineral content measurements were carried out using a XCT_960A pQCT system (Norland Medical Systems, Fort Atkinson, WI) on the proximal tibial metaphysis at 5 and 6 mm distal to the knee joint. A voxel size of 0.148 mm and a threshold of 0.600 cm for cancellous bone were used. Increasing doses of **7**-(*R*), from 0.003 to 0.3 (mg/kg)/day, were orally administered to ovariectomized rats for 6 weeks, and the density of tibial bone was measured. **7**-(*R*) effectively prevented bone loss in a dose-dependent manner. At 0.3 (mg/kg)/day, **7**-(*R*) prevented the loss of total bone density caused by ovariectomy (Figure 9). These effects were comparable to those seen with higher dose of raloxifene.[16,17]

Measurement of Serum Total Cholesterol Levels. The compound **7**-(*R*) was evaluated for the ability to reduce overall cholesterol levels. Blood samples were collected orbitally after 2 or 6 weeks of treatment. Serum samples were analyzed using a Roche Hitachi 717 chemistry analyzer at LabCorp. The effect of **7**-(*R*) on serum total cholesterol was similar in the 6-week treated animals to that seen in animals treated for 2 weeks. Plasma cholesterol levels were reduced approximately 60% after 6 weeks of treatment (Figure 10). The metabolites **5**-(*R*) and **6**-(*R*) were both effective at lowering plasma total cholesterol levels in rats following 2 weeks of treatment. **7**-(*R*) lowered plasma cholesterol about 50% at both 0.0.03 and 0.3 mg/kg.[9b]

Measurement of Weight of Vaginal Fluid. Compound **7**-(*R*) was evaluated in the rat vaginal fluidity model to assess its activity in the vagina. The fluid in vagina was collected using a cotton swab, and the absolute weight of the fluid was measured from each animal after 2 or 6 weeks of treatment. Estrogen and **5** showed the expected increase in vaginal fluidity (Figure 11). **7**-(*R*) increased the weight of vaginal fluid in OVX rats in a dose dependent manner. At the 0.1 mg/kg dose, the effect was similar to or better than that seen with 1.4 mg/kg of **5** or 0.1 mg of EE at the end of 6 weeks. Compound **5**-(*R*) was very effective at increasing vaginal secretions. This metabolite showed increased vaginal fluidity significantly at 1.0 mg/kg (Figure 12). In contrast, **6**-(*R*) and raloxifene were not effective at increasing vaginal fluidity.

Activity in the Rat Hot Flush Model. One of the important activities of an "ideal SERM" compound is the ability to reduce the incidence and severity of the hot flush, a symptom that frequently occurs in postmenopausal women. In the ovariectomized rat hot flush model, morphine-addicted rats undergo morphine withdrawal, after which they experience a "hot flush" that can be measured by their tail skin temperature. Estrogens have been shown to block this hot flush. This model has been used to characterize several SERMs including raloxifene and bazedoxifene. The effects of these compounds in this model have been predictive of clinical responses in women.[18] Adult female Sprague−Dawley rats (3 months old, Charles River Laboratories, Wilmington, MA) were used for this assay. Each treatment group consisted of 8−25 animals. They were housed individually in wire-mesh cages at an ambient temperature of 21−23 °C with an automated 12 h light/dark cycle and access to water and commercial rodent food ad libitum. The rats were ovariectomized under anesthesia. Six days after ovariectomy, treatment of the rats was initiated. Compound **9**-(*R*) or raloxifene was administered orally by gavage. The rats were injected subcutaneously (sc) with a suspension containing 75 and 150 mg of morphine (freebase) on days 3 and 5 of treatment, respectively. On the last day of treatment, the animals were lightly anesthetized with ketamine (80 mg/kg, intramuscular). Following anesthesia, a thermistor (YSI 400 series, YSI Precision Temperature Group, Dayton, OH), connected to a data acquisition system (Acquisition Interface model ACQ-10, Gould 6600 Amplifier, Gould Instrument System Inc., Valley View, OH), was placed on the tail of the animals. Following measurement of the baseline tail skin temperature for about 20 min, naloxone (2.0 mg/kg, sc, Sigma, St. Louis, MO) was administered to induce morphine withdrawal. Tail skin temperature was then measured for an additional 60 min. Multiple comparisons among the treatment groups at each time point were used for analysis. The values of area under curve (AUC) from the first 15 min following morphine withdrawal and maximal temperature change (ΔT) are reported here.[9b] Our data demonstrate that **7**-(*R*) was able to reduce the rise in tail skin temperature to an extent similar to that seen with **9**-(*R*) and EE (Figure 13). This unique pharmacological profile makes compound **7**-(*R*) an ideal clinical candidate for the treatment of hot flush.

Conclusion

We have discovered benzo[*b*]pyranobenzo[*b*]oxapines and benzopyranobenzo[*b*]oxocine as novel SERMs. Numerous derivatives of were prepared and evaluated for their biological activity as SERMs. In general, compounds with absolute configuration (*R*) are significantly more potent in antiuterotropic assays. Piperidine, thiomorpholine, and azepane are among the best side chain functional groups for antagonist potency in Ishikawa and MCF-7 cell based functional assays. Replacement of piperideine ring system by dialkyamine, like $-NMe_2$ or $-NEt_2$ resulted in strong stimulatory activity in antiuterotropic assays. Consistent with literature observations, $-OCH_2CH_2NR_2$ is the optimal side chain attached to para position to the aromatic ring. The basic amine is essential for the antagonist potency in MCF-7 and Ishikawa based functional assays. At least one hydroxy group in A ring or D ring is required for binding affinity for ERs. Compound **1a**-(*R*) and its methoxy derivatives, attached to either A ring or D ring, or dimethoxy derivatives **5**-(*R*) and **6**-(*R*) demonstrated excellent profiles in in vitro assays as well in antiuterotropic assays, and **1a**-(*R*) was selected as a candidate for in depth evaluations. Data from in vivo studies demonstrated

that **7**-(*R*) possesses an "ideal SERM profile" in animal studies and is an excellent backup candidate to our clinical candidate **9**-(*R*). It not only exhibits estrogen agonist effects on bone and lipid and antagonistic effects on mammary glands and uterus but also alleviates hot flush and increases vaginal lubrication. Full efficacy was achieved at the 0.3 mg/kg dose. This unique pharmacological profile makes compound **7**-(*R*) an ideal clinical candidate for the treatment of hot flush and vaginal dryness in postmenopausal women, without the risk of uterine or breast cell stimulation (Table 7).

Experimental Section

General Information. Optical rotations were measured on a Perkin-Elmer model 341 polarimeter. ^{1}H and ^{13}C spectra were measured on a Bruker 300, 400, or 500 MHz instrument. In the case of ^{13}C spectra, these measurements were taken with full proton decoupling. Data for proton spectra are reported as follows: chemical shifts, reported in ppm and utilizing the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, nd = narrow doublet), coupling constants (Hz). Analytical high performance liquid chromatography (HPLC) coupled with MS and UV diodray detectors was performed on an Agilent 1100 series instrument at 280 nm (UV detector) and mass ranging from 300 to 1000 (MS detector) using the following: (a) Phenonmenex, Luna 5 μm, phenylhexyl 150 mm × 4.60 mm; solvent A, H_2O (0.1% TFA); solvent B, CH_3CN (0.1% TFA); gradient 20−90% of solvent A to B; flow rate, 1 mL/min; total run time, 15 min. (b) Phenonmenex, Luna 5 μm, 150 mm × 4.60 mm; solvent A, H_2O (0.1% TFA); solvent B, CH_3CN (0.1% TFA); gradient, 20−90% of solvent A to B; flow rate, 1 mL/min; total run time, 15 min. (c) YMC diol 120, 100 mm × 4.6 mm (achiral, normal phase) column; solvent system 50% IPA in hexanes, isocratic solvent sytem; flow rate, 1 min/mL; run time, 20 min. (d) Diacel ChiralPak AD 250 mm × 4.6 mm (chiral) column using an isocratic solvent mixture, 50:50 IPA/hexanes, at a flow rate of 1 mL/min.

For thin layer chromatography (TLC) analysis throughout this work, Analtech Uniplate precoated plates were used in conjunction with a variety of developing reagents including phosphomolybdic acid (PMA) and para-anisaldehyde (PAA) in addition to UV light. Purification of materials was carried out using an ISCO chromatography system with prepacked silica gel columns. High-resolution mass spectrometry (HRMS) was performed by M-Scan, Inc., and elemental analyses were performed by QTI Technologies. All reagents and solvents were used as received from commercial source.

The following compounds were prepared using Scheme 2.

Synthesis of Compound 8a. [2-(4-Iodo-phenoxy)ethyl]piperidine (1.5 g, 4.5 mmol) was dissolved in 10 mL of THF and cooled to −78 °C. To the solution was added dropwise 1.8 mL of *n*-butyllithium (2.5 M in hexane). The solution was stirred at −78 °C for 30 min before the addition of 0.82 g (1.5 mmol) of lactal, 14 g (X2 = X1 = OTBS, n = 3)[8] in 5 mL of THF, stirred for another 30 min after the addition, quenched with aqueous ammonium chloride, extracted with ethyl acetate, and the organic layer was combined and dried over sodium sulfate.

After removal of the solvent, the crude product was dissolved in 15 mL of toluene and was cooled to 0 °C. HCl (36.5%, 0.5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was dissolved in 15 mL of THF, and 3.75 mL of 1.0 M TBAF in THF was added. The reaction mixture was stirred for 1 h, diluted with ethyl acetate, and washed with aqueous ammonium chloride and then brine. The organic layer was combined and dried over sodium sulfate. After removal of the solvent, the crude product was purified on HPLC. Purity: 97% by HPLC. LC−MS: R_f = 3.791 min. MS m/z 500 (M + 1), 522 (M + 23). ^{1}H NMR (CD_3OD) δ 1.49 (broad s, 2H), 1.69 (broad s, 4H), 1.91 (broad m, 2H), 2.08 (broad m, 2H), 2.71 (broad m, 4H), 2.92 (broad m, 2H), 3.74 (broad s, 1H), 4.12 (broad m, 2H), 4.56 (broad s, 1H), 5.95 (s, 1H), 6.08−7.65 (m, 10H). HRMS, m/z calcd for $C_{31}H_{34}NO_5$ (M + H^+) 500.2437, found 500.2439. Anal. Calcd for $C_{31}H_{35}NO_6$ (M + H_2O): C, 71.93; H, 6.82; N, 2.71; O, 18.55. Found: C, 71.92; H, 6.79; N, 2.69.

Preparation of 5-[4-(2-Dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1b. To a solution of 4.64 g of 1-[2-(4-iodophenoxy)-ethyl]dimethylamine (15.95 mmol) in 40 mL of THF at −78 °C was added dropwise 6.38 mL of *n*-butyllithium (2.5 M in hexane). The solution was stirred at −78 °C for 30 min before the solution of lactal (**14a**) (2.8 g, 5.32 mmol) in 10 mL THF was added slowly, stirred for another 30 min after the addition, and quenched with aqueous ammonium chlorideandextracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. After removal of the solvent the crude product was dissolved in 200 mL of toluene, and 1.64 mL of TFA was added. The solution was stirred for 1 h, neutralized with 5% $NaHCO_3$, and extracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. The crude product was dissolved in 50 mL of acetonitrile, and an amount of 5 mL of 70% HF in pyridine was added at room temperature. The reaction mixture was stirred overnight and diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified with flash column chromatography and eluted with 5% methanol in dichloromethane. Purity, 97% by HPLC. LC−MS: R_f = 1.98. MS: m/z, 446 (M + 1), 468 (M + 23). ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm) 7.4 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.5 (m, 2H), 6.35 (dd, ^1J = 8.4 Hz, ^2J = 2 Hz, 1H), 6.15 (d, J = 2 Hz, 1H), 6.05 (s, 1H), 4.6 (m, 2H), 4.25 (t, J = 4 Hz, 2H), 3.5 (t, J = 4 Hz, 2H), 3.3 (m, 2H), 2.9 (s, 6H). HRMS, m/z calcd for $C_{27}H_{27}NO_5$ (M^+) 445.5070, found 445.5997.

The racemic compound **1b** was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 80% IPA and 20% hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows: **1b**-(*R*) as peak 1, [α] +66° (*c* 0.402, MeOH); **1b**-(*S*) as peak 2, [α] −65° (*c* 0.5, MeOH).

Preparation of 5-[4-(2-Diisopropylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1c. Following the procedure described for **1b**, lactal **14a** (1.5 g, 2.85 mmol) was reacted in sequence with [2-(4-iodophenoxy)ethyl]diisopropylamine·HCl and then HF·Py to yield 1.1 g of the title compound as a pink solid. Purity 97%. LC−MS: R_f = 2.4. MS (m/z): MH^+ (502), MH^- (500). ^{1}H NMR ($CDOD_3$) δ 1.28 (d, 12H, J = 5.3 Hz), 2.78 (m, 2H), 3.25 (m, 2H), 3.52 (m, 2H), 4.05 (m, 2H), 4.56 (m, 2H), 6.05−7.35 (m, 11H). HRMS, m/z calcd for $C_{31}H_{35}NO_5$ (M^+) 501.2515, found 501.2515. Anal. Calcd: C, 74.23; H, 7.03; N, 2.79; O, 15.95. Found: C, 74.19; H, 7.04; N, 2.78.

The racemic 5-[4-(2-diisopropylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol compound (1.4 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 80% IPA and 20% hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows. Peak 1: 5*R*-(+)-[4-(2-diisopropylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, **1c**-(*R*). $[\alpha]_D$ +43 (*c* 0.112, MeOH). MS (m/z): MH^+ (502), MH^- (500). Peak 2: 5*S*-(−)-[4-(2-diisopropylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalene-2,8-diol, **1c**-(*S*). $[\alpha]_D$ −69 (*c* 0.812, MeOH). MS (m/z): MH^+ (502), MH^- (500).

Preparation of 5-[4-(2-Azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1d. Following the procedure as described for **1b**, lactal **14a** (1.5 g,2.85 mmol) was reacted in sequence with 1-[2-(4-iodophenoxy)ethyl]azepane, HCl, and then HF·Py to yield 1.1 g of the title compound (**1d**) as a light-yellow solid. Purity: 95% by LC−MS, R_f = 2.13. MS (*m*/*z*): MH^+ (500), MH^- (498). ^{1}H NMR ($CDOD_3$) δ 1.65 (m, 4H), 1.84 (m, 4H), 2.78 (m, 2H), 3.35 (m, 4H), 3.48 (m, 2H), 4.18 (m, 2H), 4.61 (m, 2H), 6.02 (s, 1H), 6.18−7.35 (m, 10 H). HRMS, *m*/*z* calcd for $C_{31}H_{34}NO_5$ ($M + H^+$), exact mass 500.2437, found 500.2444.

The racemic compound 5-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol (**1d**) (1.1 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 50% IPA and 50% hexanes at the 200 mL/min flow rate. The two peaks were recollected to yield the two enantiomers as follows: Peak 1: **1d**-(*R*). $[\alpha]_D$ + 33 (*c* 0.11, MeOH). MS (*m*/*z*): MH^+ (500), MH^- (498). Peak 2: 5*S*-(−)-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, **1d**-(*S*). $[\alpha]_D$ −39 (*c* 0.51, MeOH). MS (*m*/*z*): MH^+ (500), MH^- (498).

Preparation of [4-(2-Piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1a. Following the procedure as described for **1b**, lactal **14a** (1.5 g,2.85 mmol) was reacted in sequence with 1-[2-(4-iodophenoxy)ethyl]azepane, HCl, and then HF·Py to yield 1.2 g of the title compound **1a** (96% pure by HPLC). The racemic compound **1a** (1.1 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 80% IPA and 20% hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows. Peak 1: 5*R*-(+)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, **1a**-(*R*). ^{1}H NMR (CD_3OD) δ 1.46 (m, 2H), 1.59 (m, 4H), 2.55 (m, 4H), 2.72 (M, 2H), 2.81 (m, 2H), 4.02 (t, 2H, *J* = 5.4 Hz). 4.60 (m, 2H), 6.05 (s, 1H), 6.14−7.34 (m, 10H). Mp 147−149 °C. [α] +57° (*c* = 0.302, MeOH). Anal. Calcd for $C_{30}H_{31}NO_5 \cdot 0.95H_2O$: C, 71.68; H, 6.60; N, 2.79. Found: C, 71.67; H, 6.52; N, 2.57. MS (*m*/*z*): MH^+ (486). Peak 2: 5*S*-(−)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, **1a**-(*S*). [α] −59° (*c* 0.41, MeOH). MS (*m*/*z*): MH^+ (486). HRMS, *m*/*z* calcd for $C_{30}H_{32}NO_5$ ($M + H^+$) 486.5788, found 486.5783. Anal. Calcd for $C_{31}H_{35}NO_6$ (M + MeOH): C, 71.93; H, 6.82; N, 2.71; O, 18.55. Found: C, 71.92; H, 6.81; N, 2.72.

Preparation of 5-[4-(2-Morpholin-4-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1f. To a solution of 2.0 g of 1-[2-(4-iodophenoxy)-ethyl]piperidine (6.1 mmol) in 20 mL of THF at −78 °C was added dropwise 2.5 mL of *n*-butyllithium (2.5 M in hexane). The solution was stirred at −78 °C for 30 min before a solution of 1.05 g of lactal **14a** (2.0 mmol) in 5 mL of THF was added slowly, stirred for another 30 min after the addition, quenched with aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. After removal of the solvent, the crude product was dissolved in 100 mL of toluene, and 0.67 mL of 36.5% HCl was added. The solution was stirred for 1 h and neutralized with 5% $NaHCO_3$ and extracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. After concentration, the crude product was dissolved in 20 mL of acetonitrile, and 1 mL of 70% HF in pyridine was added at room temperature. The reaction mixture was stirred overnight and diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified with flash column chromatography and eluted with 5% methanol in dichloromethane. A slightly yellow solid was yielded (0.90 g, 92%). Purity: 97% by LC−MS, R_f = 2.682 min. MS *m*/*z* 488 (M + 1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 9.7 (bs, 1H), 9.55 (bs, 1H), 7.3 (d, *J* = 8.4 Hz, 2H), 7.2 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.8 (d, *J* = 8.4 Hz, 2H), 6.45 (m, 2H), 6.3 (d, ^1J = 8.4 Hz, ^2J = 2 Hz, 1H), 6.12 (d, *J* = 2 Hz, 1H), 6.1 (s, 1H), 4.55 (m, 2H), 4.0 (t, *J* = 8.4 Hz, 2H), 2.9 (m, 8H), 2.7 (m, 2H), 2.6 (t, *J* = 8.4 Hz, 2H). HRMS, *m*/*z* calcd for $C_{29}H_{30}NO_6$ ($M + H^+$) 488.2073, found 488.2079. The racemic compound **1f** (0.9 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 80% IPA and 20% hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows: **1f**-(*R*) as peak 1, [α] +27° (*c* 0.304, MeOH); **1f**-(*S*) as peak two, [α] −28° (*c* 0.41, MeOH).

Preparation of 5-[4-(2-Pyrrolidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1e. To a solution of 1.9 g of 1-[2-(4-iodophenoxy)-ethyl]pyrrolidine (6.0 mmol) in 20 mL of THF at −78 °C was added dropwise 2.5 mL of *n*-butyllithium (2.5 M in hexane). The solution was stirred at −78 °C for 30 min before a solution of 1.05 g of lactal **14a** (2.0 mmol) in 5 mL of THF was added slowly. The reaction mixture was stirred for another 30 min after the addition and then quenched with aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. After removal of the solvent the crude product was dissolved in 100 mL of toluene, and 0.67 mL of 36.5% HCl was added. The solution was stirred for 1 h and neutralized with 5% $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. After removal of the solvent, the crude product was dissolved in 20 mL of acetonitrile and 1 mL of 70% HF in pyridine was added at room temperature. The reaction mixture was stirred overnight and diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified with flash column chromatography and eluted with 5% methanol in dichloromethane. Then 0.90 g of slightly yellow solid was yielded (95% pure). LC−MS: R_f = 2.701 min, >97%, *m*/*z* 472 (M + 1). ^{1}H NMR (CD_3OD) δ 1.46 (m, 2H), 1.54 (m, 2H), 2.55 (m, 4H), 2.72 (M, 2H), 2.79 (m, 2H), 4.04 (t, 2H, *J* = 5.4 Hz). 4.60 (m, 2H), 6.15 (s, 1H), 6.14−7.34 (m, 10H). HRMS, *m*/*z* calcd for $C_{29}H_{30}NO_5$ 472.2124, found 472.2119. The
racemic compound **1e** (0.9 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 80% IPA and 20% hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows: **1e**-(*R*) as peak 1, [α] +29° (*c* 0.41, MeOH); **1e**-(*S*) as peak 2, [α] −31° (*c* 0.21, MeOH).

Preparation of 5-[4-(2-Piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, 3d. Following the procedure described for **2b**, lactal **14b** was reacted with 1-[2-(4-iodophenoxy)ethyl]piperidine (Scheme 2, X_2 = H, Y_2 = OTBS, NR_2 = $-NC_5H_{10}$[c]) to yield 2-(8-(*tert*-butyldimethylsilanyloxy)-5-{hydroxy-[4-(2-piperidin-1-ylethoxy)-phenyl]methyl}-2,3-dihydrobenzo[*b*]oxepin-4-yl)phenol **16d**, which was then treated with HCl (12 N, 4 equiv, 0.67 mL) in toluene (100 mL) to yield 1-(2-{4-[2-(*tert*-butyldimethylsilanyloxy)-11, 12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}ethyl)piperidine as a crude oil. The crude unsubstituted piperidine was then treated with HF·pyridine (70% HF, 30% Py, 0.5 mL) in CH_3CN (20 mL) at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate/THF (1:1) and then washed with 5% $NaHCO_3$ and brine. The reaction mixture was dried, concentrated, and purified by flash chromatography and eluted with 5% MeOH in DCM to yield the title compound as a slightly yellow solid. Purity 95% by LC−MS, R_f = 2.1. MS (*m*/*z*): MH^+ (470). ^{1}H NMR (acetone-d_6) δ 1.35 (m, 2H), 1.49 (m, 4H), 2.42 (br s, 4H), 2.64 (m, 2H), 2.71−2.98 (m, 3H), 3.91 (m, 2H), 4.59−4.74 (m, 2H), 6.21 (s, 1H), 6.55−7.45 (m, 11H). ^{1}H NMR (DMSO-d_6) δ 1.36 (m, 6H), 2.28−2.59 (m, 6H), 2.65 (m, 1H), 2.89 (m, 1H), 3.91 (t, 2H, *J* = 6.6 Hz), 4.59 (m, 2H), 6.16−7.38 (m, 12H), 9.65 (s, 1H). HRMS, *m*/*z* calcd for $C_{30}H_{31}NO_4$ 469.2253, found 469.2249.

The racemic 5-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol **3d** compound (800 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows. Peak 1: 5*R*-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol as **3d**-(*R*). MS (*m*/*z*): MH^+ (470). $[\alpha]_D$ +39 (*c* 0.23, MeOH). Peak 2: 5*S*-(+)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3d**-(S). MS (*m*/*z*): MH^+ (470). $[\alpha]_D$ −37 (*c* 0.43, MeOH).

Preparation of 5-[4-(2-Azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, 3c. Following the procedure described for **1b**, the lactal **14** (1.89 g, 2.0 mmol) was reacted with 1-[2-(4-Iodophenoxy)ethyl]azepane to yield 950 mg of the title compound **3c** as a yellow solid. Purity 97% by LC−MS, R_f = 3.1. MS (*m*/*z*): MH^+ (484). ^{1}H NMR (acetone-d_6) δ 1.54 (m, 8H), 2.58−2.95 (m, 8H), 3.95 (m, 2H), 4.59−4.74 (m, 2H), 6.21 (s, 1H), 6.51−7.45 (m, 11H). ^{1}H NMR (DMSO-d_6) δ 1.51 (broad s, 8H), 2.45 (broad m, 4H), 2.70 (broad m, 2H), 3.22 (broad s, 2H), 3.91 (t, 2H, *J* = 6.6 Hz), 4.56 (m, 2H), 6.15 (s, 1H), 6.39−7.36 (m, 11H), 9.67 (s, 1H). HRMS *m*/*z* calcd for $C_{31}H_{33}NO_4$ (M^+) 483.2410, found 483.2415. The racemic 5-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol compound (950 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows. Peak 2: 5*S*-(−)-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3c**-(*S*). $[\alpha]_D$ −28 (*c* 0.12, MeOH). MS (*m*/*z*): MH^+ (484). Peak 1: 5*R*-(+)-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3c**-(*R*). $[\alpha]_D$ +38 (*c* 0.25, MeOH). MH^+ (484).

Preparation of 5-[4-(2-Dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, 3a. Following the procedure described for **1b**, lactal **14b** was reacted in sequence with [2-(4-iodophenoxy)ethyl]dimethylamine·HCl and then HF·Py to yield the title compound as a yellow solid. Purity 96% by LC−MS, R_f = 2.93. MS (*m*/*z*): MH^+ (430). ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6H), 2.72 (m, 2H), 2.82 (m, 2H), 3.95 (m, 2H), 4.59 (m, 2H), 6.02 (s, 1H), 6.41−7.29 (m, 11H). ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 6H), 2.43−2.92 (m, 4H), 3.95 (t, 2H, *J* = 6.6 Hz), 4.59 (m, 2H), 6.15 (s, 1H), 6.38−7.39 (m, 11H), 9.69 (s, 1H). HRMS *m*/*z* calcd for $C_{27}H_{28}NO_4$ ($M + H^+$) 430.2018, found 430.1998.

The racemic 5-[4-(2-dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol compound (890 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 20% MeOH and 80% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows. Peak 1: 5*R*-(+)-[4-(2-dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3a**-(*R*). $[\alpha]_D$ +38 (*c* 0.3, MeOH). MS (*m*/*z*): MH^+ (430). Peak 2: 5*S*-(−)-[4-(2-dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3a**-(*S*). $[\alpha]_D$ −36 (*c* 0.32, MeOH). MS (*m*/*z*): MH^+ (430).

Preparation of 5-[4-(2-Diethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 3b. Following the procedure described for **1b**, lactal **14b** was reacted in sequence with [2-(4-iodophenoxy)ethyl]diethylamine·HCl and then HF·Py to yield the title compound as a yellow solid. Purity: 96% by LC−MS, R_f = 2.41. MS (*m*/*z*): MH^+ (458). ^{1}H NMR ($CDCl_3$) δ 1.1(m, 6H) 2.71 (m, 4H), 2.72 (m, 2H), 2.82 (m, 2H), 3.95 (m, 2H), 4.59 (m, 2H), 6.02 (s, 1H), 6.41−7.29 (m, 11H). HRMS *m*/*z* calcd for $C_{29}H_{32}NO_4$ 458.2331, found 458.2336. The racemic 5-[4-(2-diethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol compound (1.1 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 20% MeOH and 80% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows. Peak 1: 5*R*-(+)-[4-(2-diethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3b**-(*R*). $[\alpha]_D$ +42 (*c* 0.3, MeOH). MS (*m*/*z*): MH^+ (458). Peak 2: 5*S*-(−)-[4-(2-diethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo-[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3b**-(*S*). $[\alpha]_D$ −41 (*c* 0.31, MeOH). MS (*m*/*z*): MH^+ (458).

Preparation of 5-[4-(2-Azepan-1-ylethoxy)phenyl]-8-fluoro-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, 3f. The title compound was prepared according to the procedure described for **1b** starting from lactal **14d** (1.1 g). Purity 97% by LC−MS. MS (*m*/*z*): M + H = 501. ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 8H), 2.71−2.99 (m, 8H), 3.92 (t, 2H, *J* = 6.6 Hz), 4.66 (m, 2H), 6.08 (s, 1H), 6.46−7.36 (m, 10H). HRMS *m*/*z* calcd for $C_{31}H_{32}FNO_4$ 501.2315, found 501.2326. The racemic 5-[4-(2-azepan-1-ylethoxy)phenyl]-8-fluoro-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol compound **3f** (700 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 80% IPA and 20% hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows. Peak 1: 5*R*-(+)-[4-(2-azepan-1-ylethoxy)phenyl]-8-fluoro-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3f**-(*R*). $[\alpha]_D$ +24.2 (*c* 0.305, MeOH). MS (*m*/*z*): M + H = 501. Peak 2: 5*S*-(−)-[4-(2-azepan-1-ylethoxy)phenyl]-8-fluoro-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **3f**-(*S*). $[\alpha]_D$ −28.2 (*c* 0.5, MeOH). MS (*m*/*z*): M + H = 501.

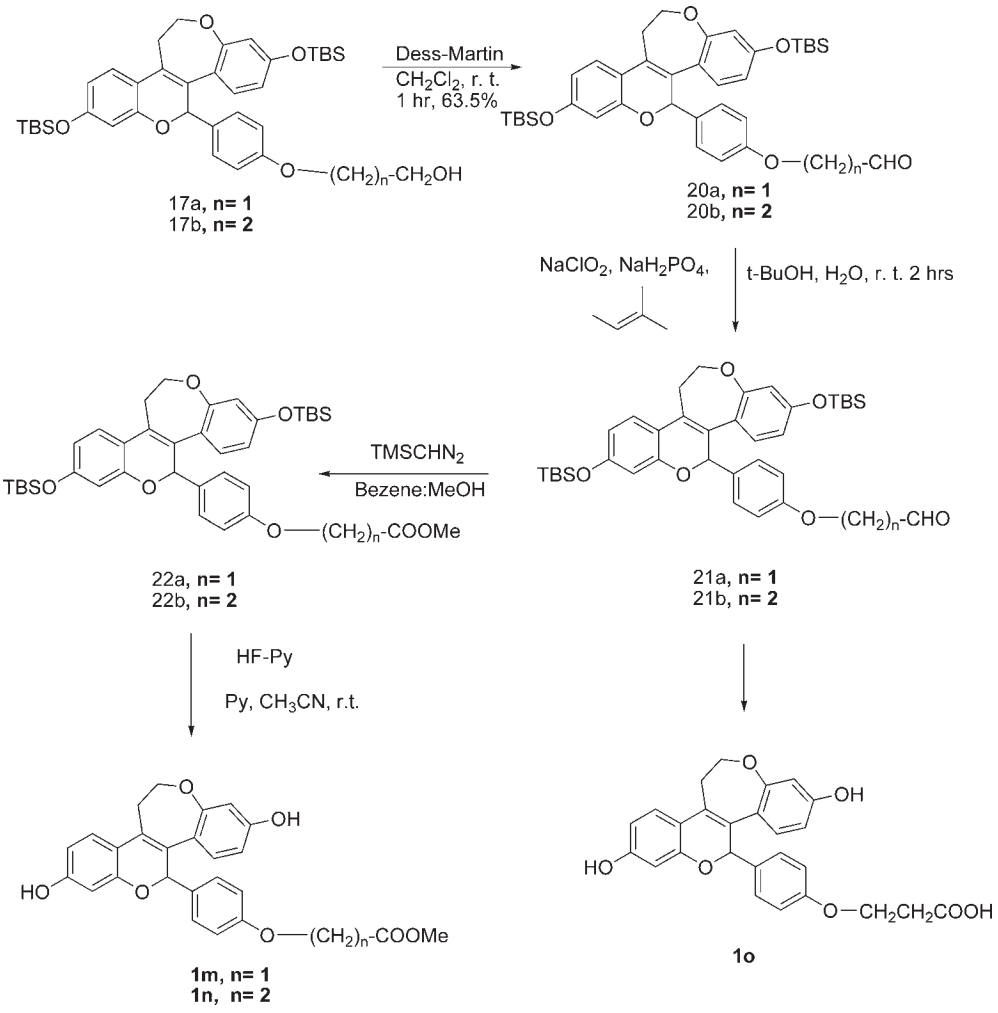
Preparation of 5-[4-(2-Dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, 4a. Following the same three-step sequence described for preparation of **1b**, lactal **14c** was reacted in sequence with [2-(4-Iodophenoxy)ethyl]dimethylamine·HCl and then HF·Py to yield the title compound **4a** as a brown solid. Purity 97%. MS (*m*/*z*): MH^+ (430). ^{1}H NMR (DMSO-d_6) δ 2.12 (s, 6H), 2.49−2.90 (m, 4H), 3.95 (t, 2H, *J* = 6.6 Hz), 4.61 (m, 2H), 6.09−7.23 (m, 11H), 9.54 (s, 1H). HRMS *m*/*z* calcd for $C_{27}H_{28}NO_4$ ($M + H^+$) 430.2018, found 430.1998.

The racemic 5-[4-(2-dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, **4a** (800 mg), was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows. Peak 1: 5*R*-(+)-[4-(2-dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo-[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, **4a**-(*R*). $[\alpha]_D$ +42 (*c* 0.34, MeOH). MS (*m*/*z*): MH^+ (430). Peak 2: 5*S*-(−)-[4-(2-dimethylaminoethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo-[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, **4a**-(S). $[\alpha]_D$ −42 (*c* 0.34, MeOH). MS (*m*/*z*): MH^+ (430).

5-[4-(2-Azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, 4b. Following the same three-step sequence described for preparation of **1b**, lactal **14c** was reacted in sequence with 1-[2-(4-iodophenoxy)ethyl]-azepane, HCl, and then HF·Py to yield the title compound **4b** as a yellow solid. Purity: 95% by LC−MS, R_f = 2.9. MS (*m*/*z*) = 483.^{1} H NMR (acetone-d_6) δ δ1.54 (m, 8H), 2.68−2.95 (m, 8H), 3.98 (m, 2H), 4.74 (m, 2H), 6.18 (s, 1H), 6.21−7.39 (m, 11H). ^{1}H NMR (DMSO-d_6) δ 1.55 (broad s, 8H), 2.68−2.92 (m, 8H), 3.92 (t, 2H, *J* = 6.6 Hz), 4.61 (m, 2H), 6.14−7.38 (m, 12H)., 9.56 (s, 1H). HRMS *m*/*z* calcd for $C_{31}H_{33}NO_4$ (M^+) 483.2410, found 483.2421.

The racemic 5-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, **4b** (840 mg), was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 40% MeOH and 60% IPA at the 100 mL/min flow rate. The two peaks were collected to yield the two enantiomers. Peak 1: 5*R*-(+)-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]

Scheme 6



cyclohepta[1,2-*a*]naphthalen-8-ol, **4b**-(*R*). $[\alpha]_D$ +37 (*c* 0.11, MeOH). MS (*m*/*z*): MH^+ (483). Peak 2: 5*S*-(−)-[4-(2-azepan-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, **4b**-(*S*). $[\alpha]_D$ −39 (*c* 0.51, MeOH). MS (*m*/*z*): MH^+ (483).

5-[4-(3-Hydroxypropoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthal ene-2,8-diol, 1l. An amount of 1.28 g of *tert*-butyl-[3-(4-iodophenoxy)propoxy]dimethylsilane (3.26 mmol) was dissolved in 10 mL of THF and cooled to −78 °C before the slow addition of 1.2 mL of 2.5 M *n*-butyllithium in hexane (3 mmol). After 1 h the lactol **14a** (400 mg) in 5 mL of THF was added slowly into the solution. The reaction mixture was stirred for another 30 min, quenched with aqueous ammonium chloride, extracted with ethyl acetate, and dried over sodium sulfate. The crude material was dissolved in 40 mL of toluene and cooled to 0 °C. Then 0.15 mL of TFA (2 mmol) was added, and the mixture was kept at 0 °C for 1 h. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. The crude material was dissolved in 10 mL of THF, and 4 mL of 1.0 M tetrabutylammonium fluoride in THF (4 mmol) was added slowly. The solution was stirred at room temperature for 1 h and worked up by washing with brine. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded a slightly orange solid, 260 mg, 60% of **1l**. ^{1}HNMR (CD_3OD, 300 MHz) δ (ppm) 7.3 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.5 (m, 2H), 6.35 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.2 (d, J = 2 Hz, 1H), 6.0 (s, 1H), 4.6 (m, 2H), 3.95 (t, J = 6 Hz, 2H), 3.7 (t, J = 6 Hz, 2H), 2.8 (m, 2H). HPLC (Luna, 5 μm C18 (2), acetonitrile−water with 0.05% TFA) t_R = 5.749, over 97% pure. HRMS *m*/*z* calcd for $C_{26}H_{24}O_6$ 432.1573, found 432.1567.

Preparation of 5-[4-(2-Hydroxyethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta [1,2-*a*]naphthalene-2,8-diol, 1k. *tert*-Butyl-[3-(4-iodophenoxy)ethanoxy]dimethylsilane (10.87 g, 30 mmol) was dissolved in 100 mL of THF and cooled to −78 °C before the slow addition of 12 mL of 2.5 M *n*-butyllithium in hexane (30 mmol). After 1 h lactol in 20 mL of THF was added slowly into the solution, stirred for another 30 min, quenched with aqueous ammonium chloride, extracted with ethyl acetate, and dried over sodium sulfate. After removal of the solvent, the crude material was dissolved in 200 mL of toluene and cooled to 0 °C. Then 0.77 mL of TFA (30 mmol) was added. The reaction mixture was kept at 0 °C for 1 h and transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. The crude material was dissolved in 100 mL of THF, and 30 mL of 1.0 M tetrabutylammonium fluoride in THF (30 mmol) was added slowly. The solution was stirred at room temperature for 1 h and worked up by washing with brine. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded slight pink crystals, 2.3 mg, 55%. ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.45 (s, 1H), 7.3 (d, J = 9 Hz, 2H), 7.2 (d, J = 9 Hz, 1H), 7.05 (d, J = 9 Hz, 1H), 6.8 (d, J = 9 Hz, 2H), 6.45 (m, 2H), 6.3 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.1 (m, 2H), 4.8 (t, J = 6 Hz, 1H), 4.45 (m, 2H), 3.9 (t, J = 6 Hz, 2H), 3.7 (m, 2H), 2.8 (m,

2H). MS: 783.3 (M + 23), 761.3 (M + 1). HPLC (Luna, 5 μm C18 (2), acetonitrile−water with 0.05% TFA) t_R = 5.749, over 97% pure. HRMS m/z calcd for $C_{25}H_{22}O_6$ 418.1416 found 418.1434.

2-{4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}-ethanol, 17a. 2-(4-Iodophenoxy)ethanol (20 g, 75.8 mmol) was dissolved in 200 mL of THF at −10 °C before the slow addition of 152 mL of 1 M isopropylmagnesium bromide in THF (152 mmol). The mixture was allowed to warm to room temperature. After 30 min 8 g (15.2 mmol) of lactol **14a** in 20 mL of THF was added slowly into the solution. After being stirred for another 30 min, the reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, and concentrated. The crude material was dissolved in 300 mL of toluene and cooled to 0 °C. TFA (1.17 mL, 15.2 mmol) was added, and the mixture was kept at 0 °C for 1 h. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded white crystals, 5.61 mg (57%) of **17a**. Chiral separation on preparation HPLC yielded, with elution with 10% isopropanol in hexane, 2.4 and 2.2 g of each enantiomer as pink crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.9 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, J = 2 Hz, 1H), 6.0 (s, 1H), 4.7 (t, J = 6 Hz, 2H), 4.0 (t, J = 6 Hz, 2H), 3.9 (m, 2H), 2.85 (t, J = 6 Hz, 2H), 1.96 (t J = 6 Hz, 1H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H). MS: 669 (M + 23), 647 (M + 1). HPLC: t_R = 5.101, >99% pure. Anal. Calcd for $C_{37}H_{50}O_6Si_2$: C, 68.69; H, 7.79, Si: 8.68. Found: C: 68.47, H: 7.67, Si: 9.32. Peak 1 as **17**-(*R*), $[\alpha]_D$ +33.5° (*c* 0.30, $CHCl_3$). Peak 2 as **17a**-(S), $[\alpha]_D$ −33.5° (*c* 0.36, $CHCl_3$).

Preparation of {4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]-phenoxy}acetaldehyde, 20a (Scheme 6). The alcohol **17a** (158 mg, 0.244 mmol) and Dess−Martin reagent (114 mg, 0.268 mmol) were dissolved in 3 mL of dichloromethane. The solution was stirred at room temperature for 1 h and then worked up by washing continuously with 5% sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel with elution with 30% ethyl acetate in hexane yielded a slightly yellow solid 100 mg (63.5%) of **20a**. ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 9.8 (s, 1H), 7.4 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 2H), 6.3 (d, J = 2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, J = 6 Hz, 2H), 4.5 (s, 2H), 2.95 (t, J = 6 Hz, 2H), 1.0 (s, 9H), 0.95 (s, 9H), 0.25 (s, 6H), 0.15 (s, 6H). MS: 645 (M + 1), 677 (M + 23). HRMS m/z calcd for $C_{37}H_{48}O_6Si_2$ 644.2989 found 644.2911.

4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}acetic Acid, 21a. To a solution of sodium dihydrogen phosphate (680 mg, 5.67 mmol) in 6.8 mL of water was added 16.7 mL of *tert*-butyl alcohol and 5.2 mL of 2-methyl-2-butene. Aldehyde **20a** (524 mg, 0.81 mmol) was dissolved in the solution, and sodium chlorite (670 mg, 7.4 mmol) was added slowly. The mixture was stirred at room temperature for 2 h, worked up by washing with aqueous sodium hydrogen sulfite, 0.1 N HCl, and brine in sequence. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude product was used for the next step without purification. MS: 661.2 (M + 1).

Preparation of {4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}acetic Acid Methyl Ester, 22a. The crude acid, **21a**, was dissolved in a mixture of 7 mL of benzene and 2 mL of methanol at room temperature followed by the addition of 1 mL of 2 M $TMSCHN_2$ in hexane. After concentration of the solvent flash column chromatography yielded 371 mg of **22a** as a colorless oil (68% for two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.4 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 2H), 6.3 (d, J = 2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, J = 6 Hz, 2H), 4.5 (s, 2H), 3.75 (s, 3H), 2.95 (t, J = 6 Hz, 2H), 1.0 (s, 9H), 0.95 (s, 9H), 0.25 (s, 6H), 0.15 (s, 6H). MS: 697 (M + 23), 675 (M + 1). HPLC: R_f = 5.182, >99%. HRMS m/z calcd for $C_{38}H_{50}O_7Si_2$ 674.3095 found: 674.299 98.

Preparation of [4-(2,8-Dihydroxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl)phenoxy]acetic Acid Methyl Ester, 1m. Di-TBS methyl ester **22a** (371 mg, 0.55 mmol) was dissolved in a mixture of 1 mL of pyridine and 5 mL of acetonitrile at room temperature. Then 0.5 mL of 70% hydrogen fluoride in pyridine was added and stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel with elution with 50−100% ethyl acetate in hexane yielded **1m** as a solid (223 mg, 91%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 9.5 (s, 1H), 9.36 (s, 1H), 7.2 (d, J = 9 Hz, 2H), 7.07 (d, J = 9 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 6.67 (d, J = 9 Hz, 2H), 6.35 (m, 2H), 6.2 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.0 (d, J = 2 Hz, 2H), 4.6 (s, 2H), 4.4 (m, 2H), 3.55 (s, 3H), 2.6 (m, 2H). MS: 469 (M + 23). HPLC: t_R = 3.039, >97% pure. HRMS m/z calcd for $C_{26}H_{22}O_7$ (M + H^+) 446.1366, found 446.1368.

3-{4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}-propan-1-ol, 17b. 3-(4-Iodophenoxy)propanol (2.78 g, 10 mmol) was dissolved in 20 mL of THF at room temperature before the slow addition of 20 mL of 1 M isopropylmagnesium bromide in THF (20 mmol). After 30 min lactol (1.05 g, 2 mmol) in 5 mL of THF was added slowly into the solution. The mixture was stirred for another 30 min, and the reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, and concentrated. The crude material was dissolved in 40 mL of toluene and cooled to 0 °C. Then 0.15 mL of TFA (2 mmol) was added and the mixture was kept at 0 °C for 1 h. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded white crystals, 610 mg (46% for two steps). Chiral separation on preparation HPLC with elution with 10% isopropanol in hexane gave each enantiomer **17b**-(*R*) as peak 1 and **17b**-(*S*) as peak 2. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.9 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, J = 2 Hz, 1H), 6.0 (s, 1H), 4.66 (t, J = 6 Hz, 2H), 4.05 (t, J = 6 Hz, 2H), 3.8 (m, 2H), 2.87 (t, J = 6 Hz, 2H), 2.0 (m, 2H), 1.7 (t, J = 6 Hz, 1H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H). MS: 683 (M + 23), 661 (M + 1). HPLC: t_R = 5.101, >97% pure. Anal. Calcd for $C_{38}H_{52}O_6Si_2$: C, 69.05; H, 7.93, Si: 8.50. Found: C: 68.68, H: 8.00; Si: 8.90. Peak 1, $[\alpha]_D$ +29.5° (*c* 0.36, $CHCl_3$). Peak 2, $[\alpha]_D$ −29.5° (*c* 0.36, $CHCl_3$).

Preparation of 3-{4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]-phenoxy}propionaldehyde, 20b. To the flask with 560 mg of the starting alcohol **17b** (0.847 mmol), 539 mg of Dess−Martin reagent (1.27 mmol), and 142 mg of sodium bicarbonate (1.69 mmol) was added 10 mL of dichloromethane. The solution was stirred at room temperature for 1 h and then worked up by washing continuously with 5% sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel with elution with 30% ethyl acetate in hexane yielded a slightly yellow solid, 384 mg (69%) of **20b**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.8 (s, 1H), 7.4 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4

(dd, ^1J=9 Hz, ^2J=2 Hz, 2H), 6.3 (d, J=2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, J=6 Hz, 2H), 4.2 (t, J=6 Hz, 2H), 2.8 (m, 4H), 0.97 (s, 9H), 0.92 (s, 9H), 0.20 (s, 6H), 0.10 (s, 6H).

Preparation of 3-{4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}propionic acid, 21b. To a solution of 487 mg of sodium dihydrogen phosphate (4.06 mmol) in 4.8 mL of water were added 12 mL of *tert*-butyl alcohol and 4 mL of 2-methyl-2-butene. Aldehyde **20b** (384 mg, 0.58 mmol) was dissolved in the solution, and 477 mg of sodium chlorite (5.2 mmol) was added slowly. The mixture was stirred at room temperature for 2 h and worked up by washing with aqueous sodium hydrogen sulfite, 0.1 N HCl, and brine in sequence. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel with elution with 20−80% ethyl acetate in hexane yielded 359 mg of a slightly pink solid (92%) of **21b**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 12.3(s, 1H), 7.3 (m, 3H), 7.1 (d, J=9 Hz, 1H), 6.8 (d, J=9 Hz, 2H), 6.6 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.55(d, J=2 Hz, 1H), 6.4 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.2 (d, J=2 Hz, 2H), 4.57 (m, 2H), 4.07 (t, J=6 Hz, 2H), 2.9−2.7 (m, 2H), 2.6 (t, J=6 Hz, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.18 (s, 6H), 0.14 (s, 6H). HPLC: 4.987 min, >95% pure. MS: 675 (M + 1). Anal. Calcd for $C_{38}H_{50}O_7Si_2$: C, 67.62; H, 7.47; Si, 8.32. Found: C, 67.05, H, 7.49; Si, 8.29. HRMS m/z calcd for $C_{38}H_{50}O_7Si_2$ 674.3095, found 674.3112.

Preparation of 3-{4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]-phenoxy}propionic Acid Methyl Ester, 22b. An amount of 187 mg of the acid (0.277 mmol) was dissolved in a mixture of 3.5 mL of benzene and 1 mL of methanol at room temperature followed by the addition of 0.21 mL of 2 M $TMSCHN_2$ in hexane. The mixture was concentrated and purified by flash column chromatography. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.4 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.6 (d, J=2 Hz, 1H), 6.55 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.4 (dd, ^1J= 9 Hz, ^2J=2 Hz, 2H), 6.3 (d, J=2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, J= 6 Hz, 2H), 4.17 (t, J=6 Hz, 2H), 3.69 (s, 3H), 2.86 (t, J=6 Hz, 2H), 2.75 (t, J=6 Hz, 2H), 0.97 (s, 9H), 0.93 (s, 9H), 0.20 (s, 6H), 0.16 (s, 6H). MS: 711 (M + 23), 689 (M + 1). HPLC: t_R = 5.280, >97% pure. HRMS m/z calcd for $C_{39}H_{53}O_7Si_2$ 689.3330, found 689.3328.

3-[4-(2,8-Dihydroxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalen-5-yl)phenoxy]propionic Acid, 1o. An amount of 90 mg of the starting di-TBS acid (0.13 mmol) was dissolved in a mixture of 0.4 mL of pyridine and 2 mL of acetonitrile at room temperature. Then 0.2 mL of 70% hydrogen fluoride in pyridine was added and stirred overnight. The mixture was diluted with ethyl acetate−THF (1:1) and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel with elution with 10% methanol in dichloromethane yielded 57 mg of a slightly pink solid (98%). ^{1}HNMR (acetone-d_6, 300 MHz) δ (ppm) 9 (bs, 1H), 7.4 (d, J=9 Hz, 2H), 7.25 (d, J=9 Hz, 1H), 7.1 (d, J=9 Hz, 1H), 6.86 (d, J=9 Hz, 2H), 6.58 (m, 2H), 6.4 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.27 (d, J=2 Hz, 1H), 6.1 (s, 1H), 4.65 (m, 2H), 4.2 (t, J=6 Hz, 2H), 2.9 (m, 2H), 2.75 (t, J=6 Hz, 2H). MS: 469 (M + 23), 447 (M + 1). HPLC: t_R = 2.891, >97% pure. HRMS m/z calcd for $C_{26}H_{23}O_7$ 447.1444, found 447.14443.

1-(2-{4-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}ethyl)pyrrolidine-2,5-dione, 19i. In a flask, 49.5 mg of succinimide (0.5 mmol) and 131.2 mg of triphenylphosphine (0.5 mmol) were dissolved in 5 mL of THF. The starting alcohol **17b**-(*S*) (323 mg, 0.5 mmol) in 1 mL of THF and 0.079 mL of DEAD in 1 mL of THF were added into the flask at the same rate by syringes. The mixture was stirred overnight at room temperature. After concentration of the solvent, flash column chromatography gave a white powder of **19i**-(*S*) (0.28 g, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.3 (d, J=9 Hz, 2H), 7.1 (d, J=9 Hz, 1H), 7.0 (d, J=9 Hz, 1H), 6.9 (d, J=9 Hz, 2H), 6.6 (d, J=2 Hz, 1H), 6.5 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.4 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.3 (d, J=2 Hz, 1H), 6.0 (s, 1H), 4.64 (t, J=6 Hz, 2H), 4.1 (t, J=6 Hz, 2H), 3.5 (m, 2H), 2.85 (t, J=6 Hz, 2H), 2.43 (m, 4H), 0.96 (s, 9H), 0.93 (s, 9H), 0.19 (s, 6H), 0.15 (s, 6H). MS: 727 (M + 23). $[\alpha]_D$ −35.5° (c 0.32, $CHCl_3$). HRMS m/z calcd $C_{41}H_{54}NO_7Si_2$ (M + H^+) 728.3439, found 728.3440.

1-{2-[4-(2,8-Dihydroxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalen-5-yl)phenoxy]ethyl}pyrrolidine-2,5-dione, 1i-(*S*). An amount of 220 mg of the **19i**-(*S*) (0.30 mmol) was dissolved in a mixture of 1 mL of pyridine and 10 mL of acetonitrile at room temperature. Then 0.5 mL of 70% hydrogen fluoride in pyridine was added and stirred overnight. The reaction mixture was diluted with ethyl acetate−THF (1:1) and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel with elution with 20−100% ethyl acetate in hexane yielded 145 mg of slightly pink solid (97%) of **1i**. ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.48 (s, 1H), 7.3 (d, J=9 Hz, 2H), 7.2 (d, J= 9 Hz, 1H), 7.05 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.6 (m, 2H), 6.3 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.1 (m, 2H), 4.55 (m, 2H), 4.05 (m, 2H), 3.68 (t, J=6 Hz, 2H), 2.86 (m, 1H), 2.7 (m, 1H) 2.5 (m, 4H). HPLC: t_R = 8.861, >95%. HPLC: t_R = 3.158, >95%. $[\alpha]_D$ −35.5° (c 0.22, $CHCl_3$). HRMS m/z calcd $C_{29}H_{26}NO_7$ (M + H^+) 500.1709, found 500.1712.

Preparation of 1-{2-[4-(2,8-Dihydroxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl)phenoxy]ethyl}-pyrrolidine-2,5-dione, 1i-(*R*). Same procedure as for **1i**-(S) and starting from alcohol **17a**-(R). $[\alpha]_D$ +35.5° (0.31, $CHCl_3$).

1-{3-[4-(2,8-Dihydroxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalen-5-yl)phenoxy]propyl}pyrrolidine-2,5-dione, 1j-(*R*). The title compound was prepared according to the procedure described for **1i** starting from alchohol **17b**-(*R*). ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.48 (s, 1H), 7.3 (d, J=9 Hz, 2H), 7.2 (d, J=9 Hz, 1H), 7.05 (d, J=9 Hz, 1H), 6.75 (d, J=9 Hz, 2H), 6.6 (m, 2H), 6.3 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.1 (m, 2H), 4.55 (m, 2H), 4.05 (m, 2H), 3.68 (t, J=6 Hz, 2H), 2.86 (m, 1H), 2.7 (m, 1H), 2.5 (s, 4H). HPLC: t_R = 2.905 >97%. HRMS m/z calcd $C_{30}H_{30}NO_8$ (M + H^+) 532.1971, found 532.1973, $[\alpha]_D$ +25.3° (c 0.61, $CHCl_3$).

1-{3-[4-(2,8-Dihydroxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalen-5-yl)phenoxy]propyl}pyrrolidine-2,5-dione, 1j-(*S*). The title compound was prepared according to the procedure described for **1i** starting from alchohol **17b**-(*S*). ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.48 (s, 1H), 7.3 (d, J=9 Hz, 2H), 7.2 (d, J=9 Hz, 1H), 7.05 (d, J=9 Hz, 1H), 6.75 (d, J=9 Hz, 2H), 6.6 (m, 2H), 6.3 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.1 (m, 2H), 4.55 (m, 2H), 3.87 (t, J=6 Hz, 2H), 3.47 (t, J= 6 Hz, 2H), 2.86 (m, 1H), 2.7 (m, 1H) 2.56 (s, 4H), 1.85 (m, 2H). HPLC: t_R = 3.232 >99%. HRMS m/z calcd $C_{30}H_{30}NO_8$ (M+ H^+) 532.1971, found 532.1969. $[\alpha]_D$ −29.3° (c 1, $CHCl_3$).

Preparation of (*S*)-2,8-Bis(*tert*-butyldimethylsilanyloxy)-5-[4-(3-iodopropoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene, 18b-(*S*). To a solution of the starting alchol **17b**-(*S*) (370 mg, 0.572 mmol) in 5 mL of DMF was added 517 mg (1.14 mmol) of methyltriphenoxyphosphonium iodide at ambient temperature. The mixture was stirred for 30 min, diluted with ethyl acetate, and washed with water and then brine. The organic layer was dried over sodium sulfate and concentrated. Then 400 mg of white solid was yielded after purification on silica gel, eluting with 10% ethyl acetate in hexane (94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, J=9 Hz, 2H), 7.1 (d, J=9 Hz, 1H), 7.0 (d, J= 9 Hz, 1H), 6.9 (d, J=9 Hz, 2H), 6.6 (d, J=2 Hz, 1H), 6.5 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.4 (dd, ^1J=9 Hz, ^2J=2 Hz, 1H), 6.3 (d, J=2 Hz, 1H), 6.0 (s, 1H), 4.66 (t, J=6 Hz, 2H), 3.96 (t, J= 6 Hz, 2H), 3.33 (t, J=6.6 Hz, 2H), 2.85 (m, 2H), 2.2 (m, 2H), 0.98 (s, 9H), 0.95 (s, 9H), 0.21 (s, 6H), 0.17 (s, 6H). MS: 793 (M + 23), 771 (M + 1). HPLC: t_R = 5.620, >98% pure. Anal.

Calcd for $C_{38}H_{51}IO_5Si_2$: C, 59.21; H, 6.67; I, 16.46. Found: C, 59.17; H, 6.67; I, 17.13. $[\alpha]_D$ +28.7° (*c* 0.36, $CHCl_3$).

Preparation of (*S*)-2,8-Bis(*tert*-butyldimethylsilanyloxy)-5-[4-(3-iodopropoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene, 18b-(*R*). The title compound was prepared according to the procedure described for **18**-(*S*), starting from alchohol **17b**-(*R*): $[\alpha]_D$ −29° (*c* 0.39, $CHCl_3$).

Preparation of 5-[4-(3-Piperidin-1-ylpropoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1p-(*S*). Step 1. To a flask was added the starting iodide **18b**-(*S*) (220 mg, 0.285 mmol), potassium bicarbonate (42.8 mg, 0.428 mmol), 42.3 μL of piperidine (0.428 mmol), and 3 mL of acetonitrile. The mixture was kept at 60 °C overnight, diluted with 100 mL of ethyl acetate, and washed with brine twice. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded 172 mg of white powder (83%). **19p**-(*S*): ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.9 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.0 (s, 1H), 4.66 (t, *J* = 6 Hz, 2H), 3.96 (t, *J* = 6 Hz, 2H), 2.85 (m, 2H), 2.4 (m, 6H), 1.9 (m, 2H), 1.55 (m, 4H), 1.42 (m, 2H), 0.97 (s, 9H), 0.94 (s, 9H), 0.20 (s, 6H), 0.16 (s, 6H). MS: 728 (M + 1). HPLC: t_R = 4.609, > 99% pure. Anal. Calcd for $C_{43}H_{61}NO_5Si_2$: C, 70.93; H, 8.44; N, 1.92. Found: C, 70.62; H, 8.68; N, 1.82. $[\alpha]_D$ −24° (*c* 0.30, $CHCl_3$).

Step 2. The starting material (150 mg, 0.21 mmol) was dissolved in a mixture of 1 mL of pyridine and 3 mL of acetonitrile at room temperature. Then 0.5 mL of 70% hydrogen fluoride in pyridine was added, and the mixture was stirred overnight, diluted with ethyl acetate−THF (1:1), and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel with elution with 0−5% methanol in dichloromethane yielded a slightly pink solid of **1p**-(*S*). ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm) 7.38 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.9 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.0 (s, 1H), 4.6 (m, 2H), 3.96 (t, *J* = 6 Hz, 2H), 2.8 (m, 8H), 2.0 (m, 2H), 1.67 (m, 4H), 1.53 (m, 2H). MS: 500 (M + 1). HPLC: t_R = 5.226, > 97% pure. HRMS *m*/*z* calcd $C_{30}H_{30}NO_8$ ($M+H^+$), $C_{31}H_{34}NO_5$ ($M + H^+$) 500.2437, found 500.2539. Anal. Calcd: C, 74.53; H, 6.66; N, 2.80; O, 16.01. Found: C, 74.48; H, 6.85; N, 2.78. $[\alpha]_D$ 14° (*c* 0.20, MeOH).

Preparation of 5-[4-(3-Piperidin-1-ylpropoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1p-(*S*). The title compound was prepared according to the procedure described for **1p**-(*S*) starting from iodide **18b**-(*R*): $[\alpha]_D$ +17° (*c* 0.24, MeOH).

Preparation of (*R*)-5-[4-(2-Thiomorpholin-4-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1g-(*R*). The title compound was prepared according to the procedure described for **1p**-(*S*) starting from iodide **18a**-(*R*). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 9.65 (bs, 1H), 9.53 (bs, 1H), 7.25−7.1 (m, 3H), 6.85 (m, 2H), 6.70 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.60 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.45−6.32 (m, 2H), 6.15 (m, 2H), 4.65 (m, 2H), 3.95 (t, *J* = 6 Hz, 2H), 2.75 (m, 1H), 2.76 (m, 5H), 2.65 (t, *J* = 6 Hz, 2H), 2.57 (m, 4H). LC−MS: 2.819 min, > 97%, *m*/*z* 504 (M + 1). HRMS *m*/*z* calcd $C_{29}H_{30}NO_5S$ 504.1845, found 504.1865. Anal. Calcd: C, 69.16; H, 5.80; N, 2.78; O, 15.88; S, 6.37. Found: C, 69.28; H, 5.79; N, 2.79. $[\alpha]_D$ +66° (*c* 0.24, MeOH).

Preparation of (*S*)-5-[4-(2-Thiomorpholin-4-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1g-(*S*). The title compound was prepared according to the procedure described for **1p**-(*S*), starting from iodide **18a**-(*S*): $[\alpha]_D$ −50.5° (*c* 1.1, $CHCl_3$).

Preparation of *R*-5-{4-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl}-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1h-(*R*). The title compound was prepared according to the procedure described for **1p**-(*S*), starting from iodide **18a**-(*R*). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 9.95 (bs, 1H), 9.83(bs, 1H), 7.65−7.18 (m, 3H), 6.95 (m, 2H), 6.80 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.80 (m, 2H), 6.32 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.15 (m, 2H), 4.55 (m, 2H), 3.95 (t, *J* = 6 Hz, 2H), 2.85 (m, 1H), 2.70 (m, 1H), 2.60 (t, *J* = 6 Hz, 2H), 2.40 (m, 4H), 2.40 (m, 4H)2.15 (s, 3H). LC−MS: 2.514 min, > 97%, *m*/*z* 501 (M + 1). $[\alpha]_D$ +66° (*c* 0.21, MeOH). LC−MS: R_f = 2.819 min, > 97% pure, *m*/*z* 501 (M + 1). HRMS *m*/*z* calcd for $C_{30}H_{33}N_2O_5$($M + H^+$) 501.2389, found 501.2411.

Preparation of *R*-5-{4-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl}-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 1h-(*S*). $[\alpha]_D$ −59° (*c* 0.61, MeOH).

2-{3-[2,8-Bis(*tert*-butyldimethylsilanyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl]phenoxy}-ethanol, 23. 3-(3-Iodophenoxy)propanol (6 g, 22.7 mmol) was dissolved in 100 mL of THF at room temperature before the slow addition of 45 mL of 1 M isopropylmagnesium bromide in THF (20 mmol). After 30 min lactol **14a** (2.37 g, 4.5 mmol) in 30 mL of THF was added slowly into the solution. After being stirred for another 30 min the reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, and concentrated. The crude material was dissolved in 200 mL of toluene and cooled to 0 °C. TFA (0.4 mL, 4.5 mmol) was added, and the mixture was kept at 0 °C for 1 h. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded white crystals 1.13 g, (77% for two steps) of **23**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.17−7.0 (m, 5H), 6.75 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.6 (d, *J* = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.35 (d, *J* = 2 Hz, 1H), 6.05 (s, 1H), 4.66 (t, *J* = 6 Hz, 2H), 4.0 (t, *J* = 6 Hz, 2H), 3.85 (m, 2H), 2.87 (m, 2H), 2.0 (t, *J* = 6 Hz, 1H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H). MS: 647 (M + 1), 669 (M + 23). HPLC: t_R = 10.740. Purity > 97% pure. HRMS cacld for $C_{37}H_{51}O_6Si_2$ 647.3224, found 647.3290. Chiral separation on preparation HPLC with elution with 10% isopropanol in hexane gave each enantiomer as crystals. Peak 1 as **23**-(*R*), $[\alpha]_D$ +51° (*c* 0.30, $CHCl_3$). Peak 2 as **23**-(*S*), $[\alpha]_D$ −51° (*c* 0.31, $CHCl_3$).

(*R*)-2,8-Bis(*tert*-butyldimethylsilanyloxy)-5-[3-(2-iodoethoxy)-phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]-naphthalene, 24-(R). To a solution of the starting material **23**-(*R*) (370 mg, 0.572 mmol) in 5 mL of DMF was added methyltriphenoxyphosphonium iodide (517 mg, 1.14 mmol) at ambient temperature, and the mixture was stirred for 30 min, diluted with ethyl acetate, and washed with water and then brine. The organic layer was dried over sodium sulfate and concentrated. Awhite solid was yielded after purification on silica gel, eluting with 10% ethyl acetate in hexane (380 mg, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.15−7.0 (m, 5H), 6.75 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.6 (d, *J* = 2 Hz, 1H), 6.53 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.05 (s, 1H), 4.6 (m, 2H), 4.15 (t, *J* = 6 Hz, 2H), 3.3 (m, 2H), 2.85 (m, 2H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H). $[\alpha]_D$ +53° (*c* 0.33, $CHCl_3$). HRMS cacld for $C_{37}H_{50}IO_5Si_2$($M + H^+$) 757.2242, found 757.2199.

(*S*)-2,8-Bis(*tert*-butyldimethylsilanyloxy)-5-[3-(2-iodoethoxy)-phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]-naphthalene, 24-(S). $[\alpha]_D$ −53.5° (*c* 0.31, $CHCl_3$).

5*R*-[3-(2-Piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 2a-(*R*). The title compound was prepared according to the procedure described for **1p**-(*S*) starting from iodide **24**-(*R*) and piperidine. ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.63 (s, 1H), 9.5 (s, 1H), 7.25−7.1 (m, 3H), 6.95 (m, 2H), 6.8 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.5(dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.45 (d, *J* = 2 Hz, 1H), 6.3 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.2 (m, 2H), 4.55 (m, 2H), 4.0 (m, 2H), 2.8 (m, 2H), 2.7 (m, 2H), 2.4 (m, 4H), 1.5 (m, 4H), 1.4 (m, 2H).

LC−MS: 2.705 min, >97%, *m*/*z* 486 (M + 1). $[\alpha]_D$ +44.8° (*c* 0.4, MeOH). HRMS, *m*/*z* calcd for $C_30H_{32}NO_5$ (M + H^+) 486.5788, found 486.5793. Anal. Calcd for $C_{31}H_{35}NO_6$ (M + MeOH): C, 71.93; H, 6.82; N, 2.71; O, 18.55. Found: C, 71.96; H, 6.86; N, 2.77.

5*S*-[3-(2-Piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 2a-(*S*). The title compound was prepared according to the procedure described for **1p**-(*S*), starting from iodide **24**-(*S*) and piperidine: $[\alpha]_D$ −46° (*c* 0.31, MeOH).

5*R*-[3-(2-Thiomorpholin-4-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 2c-(*R*). The title compound was prepared according to the procedure described for **1p**-(*S*), starting from iodide **24**-(*R*) and thiomorpholine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 9.65 (bs, 1H), 9.53(bs, 1H), 7.25−7.1 (m, 3H), 6.95 (m, 2H), 6.80 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.50 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.45 (d, *J* = 2 Hz, 1H), 6.32 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.15 (m, 2H), 4.65 (m, 2H), 3.95 (t, *J* = 6 Hz, 2H), 2.85 (m, 1H), 2.70 (m, 5H), 2.65 (t, *J* = 6 Hz, 2H), 2.57 (m, 4H). LC−MS: 2.719 min. Purity >97%, *m*/*z* 504 (M + 1). HRMS *m*/*z* calcd $C_{29}H_{30}NO_5S$ 504.1845, found 504.1865. Anal. Calcd: C, 69.16; H, 5.80; N, 2.78; O, 15.88; S, 6.37. Found: C, 69.31; H, 5.77; N, 2.77. $[\alpha]_D$ +56° (*c* 0.24, MeOH).

Preparation of 5*S*-[3-(2-Thiomorpholin-4-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 2c-(*S*). The title compound was prepared according to the procedure described for **1p**-(*S*), starting from iodide **24**-(*S*) and thiomorpholine: $[\alpha]_D$ −56° (*c* 0.43, MeOH).

Preparation of 5*R*-{3-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl}-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 2b-(*R*). The title compound was prepared according to the procedure described for **1p**-(*S*), starting from iodide **24**-(*R*) and 1-methylpiperazine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 9.65 (bs, 1H), 9.53(bs, 1H), 7.25−7.1 (m, 3H), 6.95 (m, 2H), 6.80 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.50 (m, 2H), 6.32 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.15 (m, 2H), 4.55 (m, 2H), 3.95 (t, *J* = 6 Hz, 2H), 2.85 (m, 1H), 2.70 (m, 1H), 2.60 (t, *J* = 6 Hz, 2H), 2.40 (m, 4H), 2.30 (m, 4H)2.15 (s, 3H). LC−MS: 2.514 min, >97%, *m*/*z* 501 (M + 1). HRMS *m*/*z* calcd for $C_{30}H_{33}N_2O_5$- (M + H^+) 501.2389, found 501.2459. $[\alpha]_D$ +56° (*c* 0.21, MeOH).

Preparation of 5*S*-{3-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl}-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, 2b-(*S*). The title compound was prepared according to the procedure described for **1p**-(*S*), starting from iodide **24**-(*S*) and 1-methylpiperazine: $[\alpha]_D$ −53° (*c* 0.31, MeOH).

Preparation of 5*S*-(−)-1-{2-[4-(2,8-Dimethoxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl)phenoxy]-ethyl}piperidine, 7-(*S*). 5*S*-(−)-[4-(2-Piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol, **1a**-(*S*) (1 g), was dissolved in CH_3CN/MeOH (3:1) (28 mL) and $TMSCH_2N_2$ (2 M in hexane, 10 mL, excess), and the mixture was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5% MeOH in CH_2Cl_2 to yield the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 2H), 1.59 (m, 4H), 2.49 (broad s, 4H), 2.72 (m, 2H), 2.91 (m, 2H), 3.71 (s, 3H), 3.78 (s, *x*H), 4.05 (m, 2H), 4.69 (m, 2H), 6.05 (s, 1H), 6.36−7.39 (m, 10H). Purity 97% by LC−MS, R_f = 4.1. MS (*m*/*z*): MH^+ (514). HRMS: *m*/*z* calcd for $C_{32}H_{36}NO_5$ (M + H^+) 514.2593, found 514.2603. $[\alpha]^{25}$ −7.9 (*c* 0.6 g/100 mL, $CHCl_3$).

Preparation of 5*R*-(−)-1-{2-[4-(2,8-Dimethoxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-5-yl)-phenoxy]ethyl}piperidine, 7-(*R*). 5*S*-(−)-[4-(2-Piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-2,8-diol, **1a**-(*R*) (1.1 g), was dissolved in CH_3CN/MeOH (3:1) (30 mL) and $TMSCH_2N_2$ (2 M in hexane, 11.3 mL, excess), and the mixture was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5% MeOH in CH_2Cl_2 to yield the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 2H), 1.59 (m, 4H), 2.49 (broad s, 4H), 2.72 (m, 2H), 2.91 (m, 2H), 3.71 (s, 3H), 3.78 (s, *x*H), 4.05 (m, 2H), 4.69 (m, 2H), 6.05 (s, 1H), 6.36−7.39 (m, 10H). MS (*m*/*z*): MH^+ (514). ^{13}C NMR (400 MHz, DMSO-d_6): 160.08, 159.35, 158.6, 157.3, 152.32, 130.68, 129.33, 128.85, 128.17, 125.36, 124.14, 123.19, 128.85, 128.17, 125.36, 124.14, 123.19, 117.00, 114.18, 109.67, 107.37, 106.04, 102.27, 77.84, 76.58, 65.38, 57.29, 55.18, 55.29, 54.19, 27.95, 25.5, 23.88. Anal. Calcd: C, 74.68; H, 7.05; N, 2.72; O, 15.54. Found: C, 74.71; H, 7.09; N, 2.69. Purity >98% by LC-MS, R_f = 4.4. MS (*m*/*z*): MH^+ (514). $[\alpha]^{25}$ +7.2 (*c* 0.38 g/100 mL, $CHCl_3$).

Preparation of 2-Methoxy-5*S*-(−)-[4-(2-piperidin-1-ylethoxy)-phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]-naphthalen-8-ol, 6-(*S*), and 8-Methoxy-5*S*-(−)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalen-2-ol, 5-(*S*). 5*S*-(−)-[4-(2-Piperidin-1-ylethoxy)-phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]-naphthalene-2,8-diol (10 g) **1a**-(*S*) was dissolved in CH_3CN/MeOH (3:1) (280 mL) and 1.1 equiv of $TMSCH_2N_2$ (2 M in hexane 10.2 mL), and the mixture was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5−10% MeOH in CH_2Cl_2 to yield a mixture of the title compounds as yellow foam. The mixture of compounds (2.9 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the two title compounds as follows.

Peak 1: 2-methoxy-5*S*-(−)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, **6**-(*S*). ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 2H), 1.61 (s, 4H), 2.41−3.14 (m, 8H), 3.67 (s, 3H), 4.24 (s, 2H), 4.59 (m, 2H), 6.14−7.28 (m, 11H). Purity >97 by LC−MS, R_f = 2.9. MS (*m*/*z*): MH^+ (500). HRMS calcd for $C_{31}H_{34}NO_5$ (M + H+) 500.2437, found 500.1987. Anal. Calcd: C, 74.38; H, 6.85; N, 2.80; O, 15.98. Found: C, 74.41; H, 6.91; N, 2.77.

Peak 2: 8-methoxy-5*S*-(−)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **5**-(S). ^{1}H NMR (CD_3OD) δ 1.41 (broad s, 2H), 1.59 (broad s, 4H), 2.50 (broad s, 4H0, 2.68 (m, 2H), 2.81 (m, 2H), 3.78 (m, 2H), 4.61 (t, 2H, *J* = 6.0 Hz), 6.02 (s, 1H), 6.22−7.29 (m, 10H). MS (*m*/*z*): MH^+ (500). HRMS calcd for $C_{31}H_{34}NO_5$ (M + H^+) 500.2437, found 500.1687. Purity >96 by LC−MS, R_f = 2.88. MS (*m*/*z*): MH^+ (500).

Preparation of 2-Methoxy-5*R*-(−)-[4-(2-piperidin-1-ylethoxy)-phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]-naphthalen-8-ol, 7-(*R*), and 8-Methoxy-5*R*-(−)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalen-2-ol, 6-(*R*). 5*R*-(−)-[4-(2-Piperidin-1-ylethoxy)-phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]-naphthalene-2,8-diol **1a**-(*R*) (5 g) was dissolved in CH_3CN/MeOH (3:1) (150 mL) and 1.1 equiv of $TMSCH_2N_2$ (2 M in hexane, 5 mL), and the mixture was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5−10% MeOH in CH_2Cl_2 to yield a mixture of the title compounds as yellow foam. The mixture of compounds (1.4 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm i.d. × 50 cm length) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the two title compounds as follows.

Peak 1: 2-methoxy-5*R*-(−)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-8-ol, **6**-(*R*). ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 2H), 1.61 (s, 4H), 2.41−3.14 (m, 8H), 3.67 (s, 3H), 4.24 (s, 2H), 4.59 (m, 2H), 6.14−7.28 (m, 11H). ^{13}C NMR (DMSO, 400 MHz): 159.92, 158.18, 157.78, 157.42, 152.29, 130.75, 129.35, 128.14, 125.66, 123.97, 121.67, 117.18, 111,15, 110.95, 108.75, 106.87, 102.27, 77.58, 76.53, 65.37, 57.29, 55.09, 54.29, 29.00, 25.50, 23.88 (m, 10H). Purity >96% by LC−MS, R_f = 2.9. MS (*m*/*z*): MH^+ (500). HRMS calcd for $C_{31}H_{34}NO_5$ (M + H^+) 500.2437, found 500.1987. Anal. Calcd: C, 74.38; H, 6.85; N, 2.80; O, 15.98. Found: C, 74.46; H, 6.97; N, 2.79. $[\alpha]^{25}$ +78.2 (*c* 0.88 g/100 mL, MeOH).

Peak 2: 8-methoxy-5*R*-(−)-[4-(2-piperidin-1-ylethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalen-2-ol, **6**-(*R*). ^{1}H NMR (CD_3OD) δ 1.41 (broad s, 2H), 1.59 (broad s, 4H), 2.50 (broad s, 4H0, 2.68 (m, 2H), 2.81 (m, 2H), 3.78 (m, 2H), 4.61 (t, 2H, J = 6.0 Hz), 6.02 (s, 1H), 6.22−7.29 (m, 11H). ^{13}C NMR (DMSO, 400 MHz) 159.21, 158.45, 158.41, 157.39, 152.29, 130.37, 129.29, 129.10, 128.9, 124.39, 124.131, 123.36, 116.69, 111.73, 109.11, 108.55, 107.30, 103.64, 77.74, 76.40, 65.37, 57.30, 55.17, 54.30, 28.00, 25.51, 23.88). HRMS calcd for $C_{31}H_{34}NO_5$ ($M + H^+$) 500.2437, found 500.2217. Anal. Calcd: C, 74.38; H, 6.85; N, 2.80; O, 15.98. Found: C, 74.56; H, 6.88; N, 2.91. $[\alpha]^{25}$ +36 (*c* 0.38 g/100 mL, MeOH).

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Supporting Information Available: Additional experimental procedures, NMR and X-ray data, and additional supporting data. This material is available free of charge via the Internet at http://pubs.acs.org.

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